INDEX NUMBER DEC 8 - 1931

VOL. CLXXXII, No. 6 DECEMBER, 1931 No. 717

Medical Lib.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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ESTABLISHED 1820

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OF THE MEDICAL SCIENCES

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IV. A BIOLOGIC ASSAY OF THE GASTRIC SECRETION OF PATIENTS WITH PERNICIOUS ANEMIA HAVING FREE HYDROCHLORIC ACID AND THAT OF PATIENTS WITHOUT ANEMIA OR WITH HYPOCHROMIC ANEMIA HAVING NO FREE HYDROCHLORIC ACID, AND OF THE RÔLE OF INTESTINAL IMPERMEABILITY TO HEMATOPOIETIC SUBSTANCES IN PERNICIOUS ANEMIA.*

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EXPERIMENTS have already been reported which in our opinion demonstrate the existence of an etiologic relationship between achylia gastrica and pernicious anemia, and define somewhat the nature of the mechanism involved in the production of the disease.[1,2,3,4] In the course of these observations it was found that the administration of either beef muscle or normal human gastric juice independently to suitable patients with Addisonian pernicious

* The expenses of the present investigation were borne in part by grants from the J. K. Lilly gift to the Medical School of Harvard University.

anemia had no significant effect on blood formation. On the contrary, it was observed that if under appropriate conditions an opportunity for contact between these two substances was permitted, a remission was at once brought about quite as if liver had been administered. This hematopoietic effect was demonstrated to be due in all probability to an interaction between a protein or closely related substance in the beef muscle (extrinsic factor) and a product secreted by the normal human gastric mucosa (intrinsic factor). Because of the negative effect of feeding beef muscle alone to cases of pernicious anemia it was inferred that the intrinsic factor present in the normal human gastric juice was absent from the gastric juice and other digestive secretions of pernicious anemia patients. It was not demonstrable in normal human saliva or duodenal contents free of gastric juice.

Although these observations correlate perfectly with the well-known difference between the acid content of the stomach of normal individuals and that of the vast majority of cases of Addisonian pernicious anemia, it has already been pointed out that this difference in effectiveness cannot be directly related to the lack of acid alone.[3] The nature of the intrinsic factor in the normal human gastric juice has been sufficiently defined to preclude its identification with hydrochloric acid or with any of the common enzymes of the normal stomach.[5] The unknown factor is destroyed in 5 minutes by boiling, in ½ hour by a temperature of from 70° to 80° C., or in 3 days at 40° C. The intrinsic factor of the normal gastric juice interacts with the beef muscle at neutrality, and even though freed of pepsin and rennin by adsorption methods, the gastric juice is still effective. Furthermore, neither commercial pepsin, rennin, nor any of the enzymes present in the normal human duodenal contents free of gastric juice have been found able to carry out the essential reaction with beef muscle. From these observations it is apparent that the absence of hydrochloric acid or, indeed, of any of the common enzymes from the gastric juice of the pernicious anemia patient does not explain its inability to react specifically with beef muscle as does normal gastric juice.

There is, then, no theoretical objection to our hypothesis of the nature of pernicious anemia in the observation that certain patients with the blood picture of pernicious anemia have an apparently normal gastric contents.[6,7,8,9] On the other hand, there is not necessarily any contradiction to our hypothesis in the fact that certain patients showing no evidence of the blood picture of pernicious anemia have a total anacidity and sometimes a gastric content in no respect distinguishable by the usual clinical tests from that of Addisonian pernicious anemia.[10,11,12] Nevertheless, we have desired to clarify this situation, and from a study of these seemingly contradictory exceptions to add, if possible, to the already accumulated negative evidence positive support for our hypothesis.

At the moment there seems to be no way by which to determine the presence or absence of the intrinsic factor in gastric juice, except by actual trial of its effect after incubation with beef muscle upon a patient with Addisonian pernicious anemia. The apparently normal gastric juice of 2 patients with the blood picture of Addisonian pernicious anemia has, therefore, been so studied as well as the highly abnormal gastric contents of 4 patients with a complete anacidity, of whom 1 had no anemia and 3 hypochromic anemia subsequently responding to iron.

The cases used as test subjects in the studies reported in this paper and its predecessors were all patients with classical Addisonian pernicious anemia placed on diets containing no meat, liver or kidneys. During periods of daily administration of test preparations the absence of a significant increase of reticulocytes within 10 days was regarded as evidence of a lack of hematopoietic effect, while an appropriate increase within 10 days was considered a positive result. The use of the reticulocyte phenomenon in pernicious anemia has been fully discussed by Minot and his associates,[13,14] and we have already demonstrated its applicability to this particular problem.[2,3,4] The data given in Table 1 are for alternate days only during the administration of test preparations. No attempt is made to represent the changes of red blood cells and hemoglobin beyond the actual periods of test administration, since the reticulocyte curves in cases with less than 3 million r. b. c. per c.mm. give in the space of a few days far more definite information.

Assay of the Apparently Normal Gastric Juice of 2 Patients With the Blood Picture of Pernicious Anemia Before, and of 1 of These Patients After Treatment With Liver Extract. The first of these patients, Case 39,* a man entered the hospital with a chronic irregular diarrhea (sprue) acquired in China. Despite his statement of some improvement 4 years ago on first taking ¼ pound of liver daily, he had recently begun to lose strength, although continuing this therapy. His blood at entry showed 1.51 million r. b. c. per c.mm. and was in all ways typical of pernicious anemia. Gastric analysis, however, showed a normal amount of free hydrochloric acid and enzymes. Nevertheless, as a basis for planning experiments, it was assumed that this patient, like other cases of pernicious anemia, would respond typically to either the administration of the product of an effective interaction between beef muscle and normal gastric juice or at least to a sufficiently increased amount of the active principle of liver. On this assumption, possible explanations of this patient's anemia would be, according to our hypothesis, as follows:

(1) That the patient's diet had contained an insufficient amount of the extrinsic factor, already demonstrated to be present in beef muscle, to react with the intrinsic factor of the apparently normal gastric juice. (2) That although the interaction of the extrinsic and intrinsic factors occurred in this patient, he was unable, because of the diarrhea or associated loss of assimilation power of the intestinal tract, to absorb the results of that activity. (3) That although apparently normal, the gastric juice of this

* For the details of the history and course of this and the other patients studied, see Appendix.

patient, like that of other cases of pernicious anemia, contained in reality none of the intrinsic factor shown to be present in the gastric juice of the normal individual.

The first of these possibilities was tested by giving to the patient each day for 10 days 200 gm. of nearly raw, finely ground beef muscle. The results of this therapy in Case 39, as shown in the first period of Table 1, testify to its entirely negative effect on reticulocyte formation. Since it was known from previous observations that 200 gm. of beef muscle contain a sufficient amount of the extrinsic factor to react effectively with as small an amount of normal gastric juice as 75 cc., and since gastric analysis showed an excellent secretion, the first possibility was considered to be excluded.

The second possibility, that of faulty absorption, was next examined by giving the patient in the next succeeding period of 10 days 150 gm. of raw liver daily. This dose of liver pulp has been shown to have approximately the same effect on cases of pernicious anemia as the interaction of 150 cc. of normal human gastric juice and 200 gm. of beef muscle.[3] The data given in the second period of Table 1 for this patient, Case 39, show a definite but moderate peak of reticulocytes of 7.8 per cent on the eighth day of the liver feeding from an initial level of 1.04 million r. b. c. per c.mm.* The average response of reticulocytes to be anticipated under these circumstances, according to the data of Minot and his associates,[13] is about 16 per cent. It, therefore, became evident that this patient, although not as responsive to liver as most cases of pernicious anemia, was capable of reacting at least qualitatively in the typical manner, and thus the assumption originally made from the appearance of the blood picture seemed justified. This was further evidenced by the progressive clinical improvement and the increase of red blood cells under subsequent liver extract therapy.

Since absorption of the effective principle of liver had been shown to take place, at least to some extent, the third possibility, that the gastric juice of this patient though apparently normal was in reality deficient in respect to the intrinsic factor, seemed at once to be indicated. This was confirmed by actually trying the effect of incubating the gastric juice of this patient with beef muscle *in vitro* and then administering the resulting material by stomach tube to another pernicious anemia patient with the usual achylia gastrica. The technique of securing the gastric juice was in no way different from that employed in collecting the morning fasting secretion of normal individuals after the subcutaneous injection of histamin, and has already been fully described.[3] The collections were made daily during the first period of 10 days before liver therapy was applied, and the incubation of 75 cc. of the gastric juice with 200 gm. of beef muscle was carried out in the usual manner *in vitro* at pH 7 after a previous period of incubation of the beef muscle with 5 gm. of pepsin and sufficient hydrochloric acid to give the mixture a pH of 3. The essentially negative results of the daily administration of this material to Case 40 for 10 days may be seen from an inspection of Table 1. In contrast to this appears the obviously positive effect on reticulocyte production during the immediately succeeding period of 10 days when the only change in the technique was the substitution of the same amount of gastric juice obtained from a normal fasting individual for the gastric juice of Case 39.

The second patient of this type investigated, Case 41, a man, entered the hospital because of chronic diarrhea and anemia following operations resulting in multiple intestinal anastomoses. He had once taken for a brief period Liver Extract No. 343 (N. N. R.), derived from 300 gm. of liver, daily, with what he thought was some benefit; but he had not taken

* For convenience in referring to the tables the red blood cell count of the second day of the second periods is taken as the initial figure for those periods.

any liver or liver extract for 4 months. His blood at entry showed 0.87 million r. b. c. per c.mm., and was in all ways typical of Addisonian pernicious anemia. The gastric juice, however, contained a normal amount of free hydrochloric acid and enzymes.

Again it was assumed, because of the blood picture, that the response of the bone marrow would resemble that of cases with a similar blood picture and achylia gastrica. The three possibilities as to the mechanism producing this type of anemia, referred to above, were considered and tested as in the observations on the first patient, Case 39. The daily administration of 200 gm. of beef muscle for a period of 10 days increased the reticulocyte percentage to 5.2 on the sixth day of the therapy without clinical improvement. (See Table 1.) Such a response without evidence of clinical improvement at an initial level of only 870 thousand r. b. c. per c.mm. can hardly be regarded as significant, particularly when compared to the peak of 27.1 per cent of reticulocytes on the eighth day of the immediately following 10-day period of daily administration of Liver Extract No. 343 (N. N. R.) derived from 300 gm. of liver. Again the intimation was that the gastric juice of this patient, despite its seemingly normal characteristics, contained little or none of the essential intrinsic factor. This was confirmed by the entirely negative effect of giving each day for 10 days a mixture of 75 cc. of the fasting gastric juice of this patient after the usual incubation with 200 gm. of beef muscle to a typical case of pernicious anemia, Case 42. It was thus impossible to demonstrate by two methods of experiment, shown by control observations to be adequate to the task, the presence of the essential intrinsic factor in the gastric secretions of these two patients.

Although this defect contrasted with the demonstrable presence of free hydrochloric acid, pepsin and rennin by the usual tests is striking, it is nevertheless the condition already shown to exist in the classical cases of Addisonian pernicious anemia in relapse.[2,3,4]

So far the evidence is that after adequate treatment with liver the characteristic lack of free hydrochloric acid of the stomach of nearly all patients with pernicious anemia persists.[15] However, a few cases have been found to recover the power to secrete hydrochloric acid in the stomach.[16,17] Shaw[18] has reported the case of a patient with pernicious anemia who, although previously lacking in free hydrochloric acid, was found after a spontaneous disappearance of the anemia to have free hydrochloric acid in the gastric contents. Although it is evident in the light of our observations on the nature of the intrinsic factor that the reappearance of the acid does not necessarily imply the return of the absent intrinsic factor, it seemed possible that such patients as Cases 39 and 41, both of whom had free hydrochloric acid in the gastric contents during relapse, might be more likely than the average patient to recover the ability to secrete the essential intrinsic factor.

For this reason a few days after a remission had been produced in Case 41 by the administration of liver extract the gastric juice, which since the remission had shown no change in its content of hydrochloric acid or pepsin, was incubated daily with 200 gm. of beef muscle and the resulting material administered to another untreated case of pernicious anemia, Case 48. (See Table 1.) A peak of 10 per cent of reticulocytes was produced on

the tenth day at an initial r. b. c. level of 1.92 million per c.mm. The fasting gastric juice of Case 41 was collected in the usual manner each morning after the subcutaneous injection of histamin and before the daily dose of Liver Extract No. 343 (N. N. R.), derived from 300 gm. of liver, was given to the patient. By this technique it was considered impossible for any significant quantity of the liver extract given during the previous day to remain in the stomach until the next morning. However, it seemed possible that liver extract might have been excreted in the fasting gastric juice of the patient and so itself have yielded activity otherwise clearly attributable to the mixture of gastric juice and beef muscle. In order to exclude this possibility, 150 cc. of the gastric juice of a normal subject was collected daily after histamin stimulation immediately before the daily administration of Liver Extract No. 343 (N. N. R.) derived from 600 gm. of liver. This particular gastric juice alone was given daily to a patient with pernicious anemia, Case 49, for 10 days without effect on blood formation. (See Table 1.) Subsequently, this patient, Case 49, showed a response of reticulocytes of 12 per cent on the eighth day at an initial r. b. c. level of 1.95 million per c.mm. when given daily Liver Extract No. 343 (N. N. R.) derived from 300 gm. of liver.

It is to be remembered also that we and others[3,19] have found no evidence of such an effect with the fasting gastric juice of the normal individual whose body presumably contains the active principle of liver extract in abundance. The renewed activity of the gastric juice of Case 41 could thus best be attributed to the presence of the essential intrinsic factor shown to have been absent from the gastric juice before remission was induced by liver extract.

Assay of the Apparently Defective Gastric Juice of 1 Patient Without Anemia and of 3 Patients With Hypochromic Anemia. The first of these patients, Case C, a man, was admitted to the hospital because of a neurologic condition. His blood was entirely normal with a r. b. c. count of 5.4 million per c.mm., a hemoglobin of 90 per cent (14 gm. per 100 cc.), a w. b. c. count of 7300 and a stained blood film with normal differential white blood cell count and platelets. The gastric analysis, however, showed a complete absence of a free hydrochloric acid and only a trace of pepsin. Indeed, the rate of secretion was very slow, even after the subcutaneous injection of histamin. Nevertheless, on the basis of our hypothesis, it was considered possible that this gastric juice contained the intrinsic factor since the patient had no obvious defect of blood formation. Accordingly, by prolonged daily intubation of the patient, enough gastric juice, containing a great deal of mucus, was obtained for a trial of 8 days, with a daily average of about 40 cc. of this material. Each day 200 gm. of beef muscle were incubated for 2 hours with 4 gm. of pepsin, 75 cc. of water and enough hydrochloric acid to give an acidity of pH 3. The liquefied mixture was then neutralized to pH 7, and to it the gastric juice of this patient was added just before an incubation period of 2 hours. The resulting product was administered daily by stomach tube to a typical case of Addisonian pernicious anemia, Case 46. The patient responded to this therapy with a production of reticulocytes of 12.8 per cent at an initial r. b. c. level of 1.11 million per c.mm. on the tenth day of the observation, as shown in the first period of Table 1. Nor did the substitution of identical amounts of normal human gastric juice for the highly abnormal secretion of this patient, under similar conditions of incubation and administration, produce a second rise of reticulocytes in the succeeding period of 10 days.

Obviously the meager and apparently abnormal gastric secretions of this patient, Case C, obtained under circumstances identical with those employed in the collection of normal gastric juice, also contained the intrinsic factor. It became, then, possible to see how, without contradiction to our conception of the nature of pernicious anemia, this patient could potentially maintain a normal blood.

The next 3 cases studied, A, B and D, all women, did not have normal bloods. They showed, on gastric analysis, a lack of acid and enzymes quite similar to that encountered in Addisonian pernicious anemia. Yet the anemia was patently not of that variety. The salient characteristic was a marked relative reduction of the hemoglobin in respect to the number of red blood cells. Cases A and B in general corresponded to Faber's description of chronic chlorosis,[10] complicated by poor diets and some blood loss. Case D apparently suffered from chlorotic anemia of pregnancy, described by one of us,[20] and shown to respond readily to iron. Observations made by Mettier and Minot[21] have shown that similar patients will not ordinarily respond to extracts of liver effective in pernicious anemia, and these workers have also shown, with others,[22,23] the marked effect of large doses of iron in creating prompt reticulocyte responses, increases of red blood cells and hemoglobin and clinical improvement in such patients. These 3 cases were no exception, and either subsequently to or during the collection of their gastric juice for use in the observations to be described, showed typical responses to the oral administration of iron.

On the other hand, as will be seen from an inspection of the data for 3 patients with pernicious anemia, Cases 44, 45 and 47, given in Table 1, the apparently defective gastric juice of each of the 3 patients suffering from a hypochromic type of anemia, Cases A, B and D, was able to react successfully with beef muscle. During the first period of the observations on Case 44, 50 cc. of the gastric juice of Case A, when incubated daily with 200 gm. of beef muscle, and given under the conditions described for Case 46, effected a production of reticulocytes of 10.6 per cent on the eighth day of the therapy at an initial level of 1.82 million r. b. c. per c.mm. Similarly, 75 cc. of the gastric juice of Case B, although incubated and administered daily for only 7 days with 200 gm. of beef muscle, produced a response of 18 per cent of reticulocytes on the tenth day of observation of Case 45 at an initial r. b. c. level of 1.59 million per c.mm. Again, the daily incubation of 75 cc. of gastric juice from Case D with 200 gm. of beef muscle gave, on administration to Case 47, a peak of 9.6 per cent of reticulocytes at an initial level of 1.52 million r. b. c. per c.mm. on the eighth day of the therapy. It is therefore apparent that the gastric secretions of Cases A, B and D contained the intrinsic factor. However, observations made on these test patients, Cases 44, 45 and 47, in the period of 10 days

immediately following suggest that the concentration of the intrinsic factor was not equal in all of them to that of the normal human gastric juice. In the observations on Cases 44 and 47 secondary rises of reticulocytes of 12.6 and 7.8 per cent occurred respectively in response to the daily incubation of normal human gastric juice equivalent in amount to the quantity of the secretions of Cases A and D used during the immediately preceding periods. This phenomenon indicates clearly a greater potency of the normal gastric juice than of the juice of 2 of these 3 patients with hypochromic anemia.[3,13] However, it is interesting that the absence of a secondary rise of reticulocytes in Case 45 indicates no greater potency of the normal human gastric juice than of that derived from Case B, who, like all 4 of the patients of this group, had no free hydrochloric acid in the gastric contents. The properties of the gastric juice of the 6 patients studied, as described above, are summarized in Table 2.

The Factor of Intestinal Impermeability. The many instances reported in the literature of chronic diarrhea, partial obstructions or short circuits of the intestines associated with pernicious anemia[8,24] originally suggested to us the third possible mechanism of deficiency, namely, difficulty in the assimilation or further metabolism of the hematopoietic substance formed by the interaction of the intrinsic and extrinsic factors.[4] This explanation of the mechanism of the deficiency in the reported cases of this type appeared to be reasonable from the fact that in certain of them the gastric contents was stated to contain free hydrochloric acid.[8,9] The 2 cases reported in this paper as having a blood picture of pernicious anemia with an apparently normal gastric contents, Cases 39 and 41, seemingly fall into this clinical category. As did many of the reported cases, these 2 individuals suffered from persistent irregular diarrhea; in Case 39 associated with sprue and in Case 41 following repeated operations on the intestines. The effect of diarrhea in preventing the normal assimilation of liquids and food is well known. It thus originally seemed possible that chronic dysfunction of the bowel of both cases, indicated or induced by diarrhea, might have resulted in a disturbance of its absorptive capacity; a reduction of the absorbing surface was undoubtedly caused by the multiple operations in Case 41. These facts offered obvious grounds for a consideration of the possibility of defective absorption as the sole mechanism of the deficiency both in those cases already reported in the literature and in these 2 patients. Nevertheless, in these 2 particular patients before treatment clear evidence of a lack of the intrinsic factor of the gastric juice was obtained, and they were thus shown in that respect to be no different from the cases with achylia gastrica already studied.

However, it cannot be assumed from this that defective assimilation was not involved in certain of the other reported cases, or to

TABLE 1.—DIFFERENTIATION OF TYPES OF ACHYLIA ON BASIS OF INTRINSIC FACTOR.

First Periods.

Daily administration of various substances as indicated below.

Days of treatment.	Beef muscle, 200 gm.		Beef muscle incubated with g. j. Case 39.		Beef muscle, 200 gm.		Beef muscle incubated with g. j. of Case 41. †Before remission.		Beef muscle incubated with g. j. of Case 41. †After remission.		Normal g. j. man given L. E. No. 343 (600 gm.).		Beef muscle incubated with g. j. Case A.‡		Beef muscle incubated with g. j. Case B.‡		Beef muscle incubated with g. j. Case C.§		Beef muscle incubated with g. j. Case D.‖	
	Case 39.*		Case 40.		Case 41.**		Case 42.		Case 48.		Case 49.		Case 44.		Case 45.		Case 46.		Case 47.	
	R.B.C. mils.	Ret. %	R.B.C. mils.	Ret. %	R.B.C. mils.	Ret. %	R.B.C. mils.	Ret. %	R.B.C. mils.	Ret. %	R.B.C. mils.	Ret. %	R.B.C. mils.	Ret. %	R.B.C. mils.	Ret. %	R.B.C. mils.	Ret. %	R.B.C. mils.	Ret. %
0 . .	1.65	0.8	1.05	0.6	0.87	0.2	0.97	1.4	1.92	2.4	2.05	0.4	1.82	2.2	1.59	2.4	1.11	0.0	1.52	1.6
2 . .	1.32	0.2	1.07	0.8	0.89	1.6	1.25	5.3	2.08	1.4	2.34	0.1	1.64	2.8	1.45	1.6	1.35	0.6	1.37	1.0
4 . .	1.68	1.4	0.87	0.6	0.93	1.4	1.22	1.2	1.83	4.4	2.54	0.1	1.84	3.8	1.18	2.6	1.45	1.4	1.62	1.4
6 . .	1.52	0.6	0.91	2.1	0.86	**5.2**	1.33	0.6	2.01	7.2	2.18	0.1	1.60	4.4	1.46	7.2	1.19	6.8	1.44	3.8
8 . .	1.45	1.2	0.97	1.5	0.89	3.4	1.32	0.8	2.30	**10.0**	1.92	0.1	1.86	**10.6**	1.51	14.6	1.38	8.2	1.35	**9.6**
10 . .	1.28	0.2	..	..	..	..	1.28	1.0	2.45	7.4	2.01	0.6	1.87	8.0	1.44	**18.0**	1.54	**12.8**	1.77	7.2

Second Periods.

Daily administration of various substances as indicated below.

	Raw liver, 150 gm.		Beef muscle incubated with normal gastric juice.		Liver Ext. No. 343 (300 gm.).†						Liver Ext. No. 343 (300 gm.).		Beef muscle incubated with same amounts of normal gastric juice as in first periods.							
2 . .	1.04	1.2	0.79	2.8	0.85	3.8	..	..	..	..	1.95	0.2	1.73	8.8	1.74	14.4	1.52	6.0	1.77	3.3
4 . .	1.23	1.0	1.22	5.8	0.88	3.6	..	..	..	..	1.90	0.2	1.88	7.2	2.13	6.0	1.98	7.8	1.75	1.4
6 . .	1.19	5.0	0.92	14.0	0.85	17.4	..	..	..	..	1.90	5.6	2.16	5.6	2.50	2.0	2.21	5.4	1.79	1.4
8 . .	1.34	**7.8**	1.39	**14.4**	0.91	**27.1**	..	..	..	..	2.12	**12.0**	2.42	8.0	2.31	2.6	2.23	4.6	2.29	6.5
10 . .	1.40	2.4	1.82	10.2	1.26	10.2	..	..	..	..	2.87	6.0	2.47	**12.6**	2.09	1.6	2.33	3.8	2.38	**7.8**
12 . .	..	..	1.65	6.2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2.21	6.8

*Case 39: Chronic tropical sprue with blood typical of pernicious anemia. Free HCl and enzymes present in gastric juice.
** Case 41: Multiple intestinal anastomoses, blood typical of pernicious anemia. Free HCl and enzymes present in gastric juice
† Remission induced by Liver Extract No. 343.
‡ Cases A and B: Chronic chlorosis with absent HCl and enzymes. Subsequent response to iron.
§ Case C: Idiopathic achylia without anemia. Absent HCl and enzymes.
‖ Case D: Chlorotic anemia of pregnancy with absent HCl and enzymes. Subsequent response to iron.

a certain extent in Cases 39 and 41. Indeed, from the original observations on these 2 patients suggestive evidence of difficulty with the assimilation of the active principle of liver extract was obtained. Case 39 showed less than the normal response of reticulocytes, yielding only 7.8 instead of a theoretical 16 per cent of reticulocytes at an initial level of 1.04 million r. b. c. per c.mm. from the daily ingestion of 150 gm. of raw liver.[13] Although it is possible that the effect of the previous daily ingestion of $\frac{1}{4}$ pound of liver, which was discontinued only 10 days before this observation, was responsible for the relatively slight increase of reticulocytes, this seems unlikely since the patient became progressively more anemic while on the former régime. Furthermore, both Cases 39 and 41 subsequently showed an unusually slow increase of red blood cells in response to large doses of liver extract, although the diarrhea was well controlled by opiates and there was no evidence of infection or marked arteriosclerosis. It therefore seemed probable that in

TABLE 2.—PROPERTIES OF GASTRIC JUICE ASSAYED FOR INTRINSIC FACTOR.

Case No.	Diagnosis.	Free HCl (N/10 HCl/100 cc.).	Pepsin.	Rennin.	Lipase.	Intrinsic factor.
	Normal	50	15	100–200	1–2	+
39	P.A. (sprue)	10–70	17	66–333	2	0
41	P.A. (intestinal)	52–83	15	110–166	...	0
C	Comb. sys. dis.	0	2.7	...	...	+
A	Chr. chlorosis	0	1	1–2	0	+
B	Chr. chlorosis	0	4	1–2	0	+
D	Chr. chlorosis	0	6	...	...	+

addition to the absence of the intrinsic factor from the superficially normal gastric juice of these 2 patients, there was also a defect of absorptive power which would have made difficult the assimilation of the hematopoietic substance had it been formed in the stomach.

The existence of intestinal impermeability to the hematopoietic products of gastric activity originally suggested by us[4] as having bearing on the etiology of certain cases of pernicious anemia appears even more plausible from the work of Gänsslen.[25] He first showed the remarkably increased effectiveness of the active principle of liver when given intramuscularly instead of by mouth. Schilling[26] has confirmed his observations, and his work corroborates the suggestion of Cohn, McMeekin and Minot,[27] that intestinal impermeability to the active principle may account for certain of the so-called "liver resistant" cases of pernicious anemia. Our studies of the active principle of the gastric mucosa have shown it to have entirely different properties from the active principle of liver, and in all probability to be identical with the hematopoietic product of the interaction of the extrinsic and intrinsic factors of normal human

gastric digestion.[3] Recently Ederle, Kriech and Gänsslen[28] have obtained satisfactory results with the daily intramuscular administration of an extract derived from 4 gm. of gastric mucosa in contrast to the usual necessary oral dosage of 150 or more grams daily. Independently of these workers we have shown that extract derived from 100 gm. of liver when intravenously administered will produce reticulocyte responses ordinarily equalled only by the oral administration of extract derived from 1500 to 3000 gm. of liver.[29] To what extent this difference involves a normal physiologic factor is unknown, but our own preliminary observations with intravenously

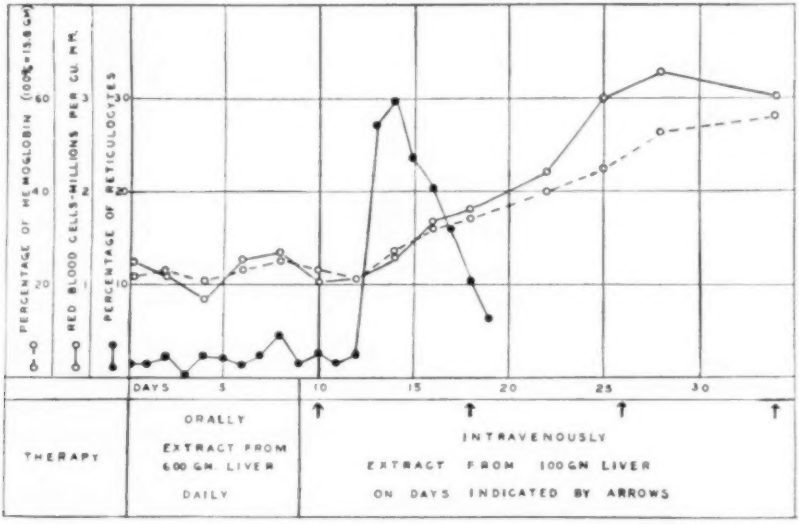

FIG. 1.—Intestinal impermeability to liver extract as illustrated by observations on a patient with pernicious anemia, Case 41.

Daily oral administration of potent liver extract derived from 600 gm. of liver was without effect on blood formation. A single intravenous injection of extract derived from 100 gm. of liver then produced a peak of 29.8 per cent of reticulocytes on the fifth day from an initial r. b. c. level of 1 million per c.mm.

administered liver extract make it evident that the effectiveness of the utilization of orally administered liver extract is a variable condition among cases of established pernicious anemia. Specifically, in Case 39, a year after the original remission described above, potent extract from 600 gm. of liver, given daily by mouth, was not sufficient to maintain a constant blood level of a little over 1 million r. b. c. per c.mm. Nevertheless, a single intravenous injection of extract derived from 100 gm. of liver produced a reticulocyte response of 29.8 per cent on the fifth day after the injection at an initial r. b. c. level of 1 million per c.mm. and a gain of almost 1 million r. b. c. per c.mm. within a week. (Fig. 1.) Since the effect of the

hematopoietic product of the interaction of the extrinsic and intrinsic factors closely resembles that of the active principle of liver, it is a reasonable assumption that the absorption of the former might be similarly embarrassed in certain cases of pernicious anemia. At some stage in the development of the disease this defect might limit the subsequent absorption of the hematopoietic product of the interaction between the extrinsic and any intrinsic factor present in the stomach of the patient.

Discussion. It may be considered that because of the relatively small number of patients forming the basis of the observations reported in this paper, little discussion of the results is possible. It should be noted, however, that the methods employed have been subjected to severe test over a period of years and that the control observations essential to the interpretation of the present experiments are based on the previous study of many patients.[2,3,4,5] Two of the observations reported in this paper were made upon patients, Cases 39 and 41, who had the blood picture of pernicious anemia but an apparently normal gastric juice. The observations showed that the gastric juice of these 2 patients, as of those with achylia gastrica, was defective in respect to the intrinsic factor found in the gastric juice of the normal individual. Since we have shown that the properties of the intrinsic factor are not those of hydrochloric acid or of pepsin or rennin, and that its specific activity with beef muscle cannot be replaced by any of those substances alone or in combination,[5] it is evident that no exception to our former observations on the etiology of pernicious anemia with achylia gastrica is offered by these cases with an apparently normal gastric juice.

On the other hand, it is not necessary to suppose that because the vast majority of cases of pernicious anemia show a gastric anacidity, a lack of acid is always evidence of an absence of the intrinsic factor which we believe to be the specific defect in pernicious anemia. This point is made very clear by the observations on the gastric juice of 4 patients, Cases A, B, C and D, who plainly did not have pernicious anemia but whose gastric contents contained no free hydrochloric acid even after the subcutaneous injection of histamin. The apparently abnormal gastric juice of these patients, indistinguishable by tests for acid or enzymes from that of many cases of pernicious anemia, nevertheless contained sufficient of the intrinsic factor to react positively with beef muscle. Indeed, the gastric juice of Cases B and C was not demonstrated to contain less of the essential intrinsic factor than similar quantities of normal human gastric juice. Case C had no anemia and thus, perhaps, corresponds to a certain number of normal individuals who have been found to have no acid in the gastric contents.[30,31] Cases A, B and D had hypochromic anemia in association with which gastric anacidity is frequently found.[12,20] Nevertheless, each had a gastric content potentially able to carry out the necessary reaction with

beef muscle to form the substance capable of relieving typical cases of pernicious anemia. For that reason we believe that they themselves showed no evidence of pernicious anemia despite the superficial resemblance of their gastric juice to that of cases of Addisonian pernicious anemia.

We have already discussed in the light of our earlier observations the ways in which a deficiency of the effective principle might theoretically be brought about and so condition certain individuals for pernicious anemia. In brief, it is obvious that an absence of one or both of the factors of the specific reaction or an inability of the body to use the product of their interaction might produce in different ways the same final defect. The aversion of many patients with pernicious anemia to meat for long periods before the development of the disease[32] suggests that their diet may have been partially or wholly lacking in the extrinsic factor shown to occur in beef muscle. The absence of the intrinsic factor from the gastric contents of pernicious anemia patients with achylia gastrica has already been inferred from the negative effect of feeding beef muscle alone to these patients, in experiments reported in the previous papers of this series.[2,3,4] Similar observations on Cases 39 and 41 further corroborated our already extensive negative evidence for that inference. Positive confirmation by direct experiment has, however, now been obtained from observations of the negative effect of incubating the apparently normal gastric contents of these 2 pernicious anemia patients with beef muscle *in vitro*. *Thus far, then, all the cases of pernicious anemia in relapse which have been examined by us have failed to show the intrinsic factor no matter what was the apparent condition of their gastric juice.*

It is, of course, not necessarily certain that the mechanism lacking at one time in a given patient is lacking at all times. A few days after a remission had been produced in Case 41 by the administration of liver extract the gastric juice of this patient was again tested for the presence of the intrinsic factor. In contrast to the negative effect obtained with the gastric juice secreted before the remission, the gastric juice obtained thereafter was found to react positively with beef muscle. (Table 1.) It is therefore probable that after remission the gastric juice of this patient, Case 41, contained the intrinsic factor as does the gastric juice of normal individuals, and therefore reacted positively with the beef muscle in a similar way. A recovery of the ability to secrete free hydrochloric acid has been observed in a few patients with pernicious anemia after treatment with liver.[16,17] Bloomfield and Pollard[33] have reported an improvement in the gastric secretion of a case of sprue after treatment, and Chang, Yang and Keefer[34] have observed an increase in the amount of hydrochloric acid secreted by certain cases of "secondary" anemia after treatment was instituted. Of course, in the light of our observations the reappearance of hydro-

chloric acid in the gastric secretions does not necessarily indicate the recrudescence of the essential intrinsic factor, but it does demonstrate an improvement of a function which is frequently lost in association with loss of the power to secrete the intrinsic factor. On the other hand, the usual failure of hydrochloric acid to reappear in the stomach of the case of pernicious anemia which has been treated *does not exclude* the possibility of an undetected improvement of the capacity of the stomach to secrete the *essential* intrinsic factor.

By the experiments reported above, an adequate criterion has been applied for the first time to the determination of the presence or absence of the intrinsic factor in the gastric juice of human beings, and so in our opinion a true measure taken of their immediate predisposition to pernicious anemia. The essential intrinsic factor, with or without a lack of free hydrochloric acid, has been found to be absent from the gastric contents of all patients with pernicious anemia in relapse so far examined and to be present in the similarly acid- and enzyme-free gastric contents of an otherwise normal individual, Case C, and of 3 patients with hypochromic anemia, Cases A, B and D. (Table 1.) There is, then, no paradox in the fact that a lack of free hydrochloric acid has been reported in normal young adults.[30] Nor is the fact that there may be an absence of free hydrochloric acid from the gastric juice of certain pernicious anemia patients for several years before the appearance of the anemia[35] inconsistent with our hypothesis. Moreover, as there seems to be a certain degree of correlation between a lack of the intrinsic factor and of free hydrochloric acid, and as gastric anacidity in normal individuals has been shown to occur with increasing frequency with advancing years,[36] we can perhaps now understand why the age incidence of pernicious anemia should be late rather than early in life. It is thus evident that the ability of the individual to carry out the specific reaction between the extrinsic and the intrinsic factors might decline with a progressive loss of the intrinsic factor over a period of years, with no obvious change in the ordinary clinical chemistry of the gastric contents.

Since gastric anacidity does not necessarily indicate a lack of the specific intrinsic factor and is commonly found in cases of idiopathic hypochromic anemia, it is now not difficult to understand the association of this type of anemia with pernicious anemia in those families known to show a high incidence of achlorhydria among their members,[37,38] some of whom may even show no evidence of faulty blood formation of any kind. Indeed, all these possibilities may even be successively represented in the history of a single individual, who may first show no anemia, secondly, an anemia of the hypochromic variety and, finally, a true pernicious anemia.[39] In the light of our observations such a sequence of events could be interpreted most simply on the basis that the pernicious type of anemia did not develop until the essential intrinsic factor had become

sufficiently diminished. For this to occur no change in the degree of achlorhydria need, of course, be manifest, since in the totally anacid gastric juice of Cases B and C a normal amount of the essential intrinsic factor was demonstrable, in Cases A and D a reduced amount was found, and in the typical cases of pernicious anemia none. *It therefore follows that unless a specific test is made it cannot be positively known whether the intrinsic factor is present or absent in any individual at any time no matter what is the condition of the gastric juice in other respects.*

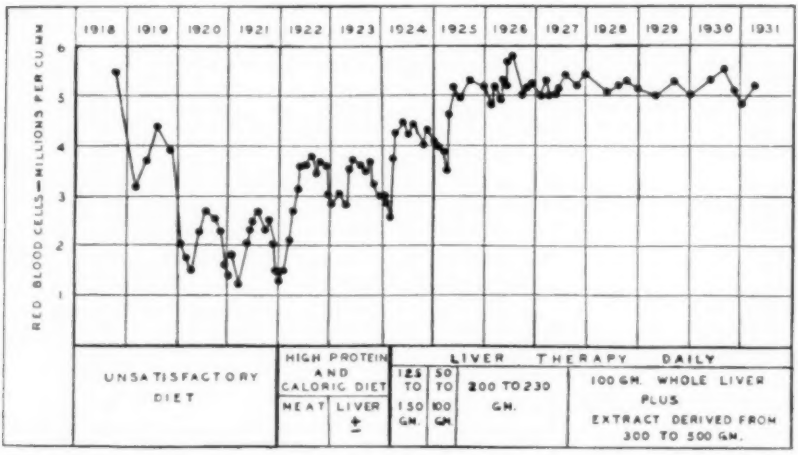

FIG. 2.—Red blood cell counts of a patient with pernicious anemia followed by Dr. George R. Minot over a period of 14 years.

During the years 1918 to 1921, while taking an unsatisfactory diet the red blood cell counts showed a progressive descent, with the lowest counts in the winter and the highest in the summer. During 1922 the patient was placed on a high caloric diet containing much animal protein (extrinsic factor) and the red blood cell counts averaged 1 million higher than during the 2 preceding years. In 1923 the patient began to take a little liver and later when placed on increasing amounts attained a normal red blood cells count which has been maintained for 7 years.

The tendency of the condition of patients with pernicious anemia to show "spontaneous" fluctuations has been frequently remarked in the past. The oscillating and progressive descent of the red blood cell count of a patient observed over a period of years by Dr. George R. Minot is clearly illustrated in Fig. 2,* as well as the subsequent effect of continued liver feeding in permanently maintaining the blood count of the patient at a normal level. The annual depression of the level of the blood counts of this patient before treatment is strikingly seasonal, as in the relapses during treatment reported by Isaacs.[40] The number of untreated or relapsed cases of

* Permission to present these data was kindly given the authors by Dr. George R. Minot.

this disease admitted to the Boston City Hospital during the winter months is somewhat greater than during the summer months. Seasonal fluctuations in the incidence of deficiency diseases, such as epidemic hemeralopia,[41] pellagra[42] and scurvy,[43] may be attributable to variations in diet factors. On the basis of our explanation of the immediate causes leading to the development of pernicious anemia, it is evident that fluctuations either in the amount of the extrinsic factor in the diet or of the amount of intrinsic factor secreted by the stomach could cause variations in the amount of hematopoietic substance formed as a result of the interaction of these two factors. Moreover, we have presented evidence that after the administration of hematopoietic substance in the form of liver extract added to the diet, the intrinsic factor, known to be absent before this therapy, reappeared in the gastric juice of Case 41. Under these circumstances the essential function of the stomach of this patient was improved after the administration of the hematopoietic factor, perhaps thus representing a chemical improvement of the function of the gastrointestinal tract just as the reappearance of the papillæ on the tongue of certain patients after treatment with hematopoietic substance represents a morphologic repair.[44] This seems to us an observation of potentially great significance in its bearing on the explanation of the "spontaneous" fluctuations characteristic of the disease before its voluntary control was possible.

On this basis it is evident that if a patient in the early stages of pernicious anemia still had a certain amount of intrinsic factor in the gastric secretion an increase of the extrinsic factor in the diet would not only immediately increase the amount of the hematopoietic substance formed, but that the increase of the latter so brought about might shortly increase the secretion of the intrinsic factor. This, in turn, would lead to a still further increase of the formation of the hematopoietic product. On the contrary, if the extrinsic factor were diminished a decreased formation of the hematopoietic product would result and possibly later of the intrinsic factor. Due to this interaction of factors an unstable equilibrium peculiar to the conditions of the disease would obviously be created, with a tendency to proceed in one direction or the other beyond effects referable directly to variation in the amounts of extrinsic factor. Since in the fully developed disease less hematopoietic substance is necessary to maintain a low red blood cell level than a high one,[14,45] these marked fluctuations would not necessarily be either immediately disastrous or entirely curative. Even a reduced amount of hematopoietic product might for a time be sufficient to maintain a red blood cell count at a low level. On the other hand, since a normal red blood cell count could not be so easily maintained as one at a somewhat lower level, the patient would not necessarily regain an entirely normal blood even with a marked relative increase in the formation of the hematopoietic substance. Finally, with

the complete disappearance of the intrinsic factor, which we have found to be the case in all the patients with the fully developed disease, blood production would fall to a level incompatible with life.

This general explanation of the natural course of the disease is further suggested by the fact that before treatment with liver was used the most successful management of the patients seemed to be attained by the use of diets rich in animal protein,[46,47] and so probably containing much of the extrinsic factor. The effect of such a régime is shown by the distinct improvement of the blood level of a case of pernicious anemia after the institution of this treatment. (Fig. 2.) Since with the beginning of a remission the patient's appetite improves and the tendency is to eat more, the intake of of extrinsic factor would rise still further, while the ability of the body to utilize it in the formation of the hematopoietic substance might also improve. The evidence by analogy with the seasonal incidence of other deficiency diseases suggests that the "spontaneous" remissions and relapses were really due to slight fluctuations in the amount of the extrinsic factor in the food, thereafter effective in a magnified way in producing fluctuations in the red blood cell counts by the mechanism we have outlined. Of course, other general systemic conditions such as infections might affect the amount of secretion of the intrinsic factor[48] or even operate directly upon the bone marrow.[49] In contrast to the earlier natural history of the disease observed by others, we have seen in the course of observations on over 100 patients with pernicious anemia, under conditions in the hospital such that their intake of the extrinsic factor was controlled and probably small, only one striking "spontaneous" remission. It is possible that the periods of controlled observation of from only 10 to 40 days which we have used were not sufficiently long to provide opportunity for improvement such as occurred during the prolonged periods of rest and bed care formerly given these patients. It is, however, readily comprehensible that before the liver treatment of pernicious anemia remissions were common and inexplicable, since the mechanism which we believe to have an important bearing on this phenomenon was not then known, and so the essential factor not controlled.

APPENDIX OF CASE HISTORIES.

Case 39.—R. W., aged 55 years, white, married, an American minister. Diagnosis: Sprue; chronic diarrhea; pernicious anemia. Admitted, March 24, 1930. Discharged, May 5, 1930.

Pertinent History. Ever since the patient was engaged in missionary work in China, 28 years ago, he had had spells of diarrhea, anemia and weakness. The stools at first, and sometimes after, were grayish, foamy, often contained mucus and sometimes blood. At the time of onset he also had malaria with recurrence of chills every fall. Seven years ago he was told that he had sprue and was given a diet containing some liver. Temporary improvement followed, but later he began to lose weight again and developed a sore tongue and sores within his nose. Four years ago he returned to the United States and was placed on a diet containing ¼ pound of liver and 3 yeastcakes daily. On this régime he gained strength, until 4 months before entry, when he began to grow weaker, paler and to have more diarrhea, some palpitation on exertion and swelling of the ankles. He had had no paresthesias.

Admission Examination. The patient was a tall, somewhat emaciated, pale, white-haired man. The scleræ were clear and not jaundiced. The tongue was quite atrophic around the edges. The upper teeth were replaced by a plate and there were many false lower teeth. The lungs were negative. The heart showed a systolic murmur. The blood pressure was 125 systolic and 55 diastolic. The vessels were normal. The abdomen was negative. The deep reflexes were normal. The vibration sense was slightly diminished over the tibiæ.

Laboratory Reports. Urine: Negative. *Stools:* Soft, light brown, no foam. Odor not offensive. Occult blood test, negative. No ova or amœbae on inspection or culture. *Blood:* R. b. c., 1,510,000; w. b. c., 2650; hemoglobin, 39 per cent (Sahli); color index, 1.28. Differential: Polymorphonuclears, 40; lymphocytes, 48; mononuclears, 8; eosinophils, 4; basophils, 0 per cent. The red cells showed marked variation in size and shape, there being both microcytes and macrocytes and occasional basophilic cells. Nucleated red cells were rare. Platelets were normal in number, but occasionally a very large platelet was seen. *Gastric analysis:* Fasting contents, 60 cc. of slightly yellowish material containing no food; free HCl, 10; total acidity, 30. After 100 cc. of 7 per cent alcohol, at 20 minutes: free HCl, 27; total acidity, 59; at 40 minutes: free HCl, 53.5; total acidity, 60. After 0.5 mg. of histamin subcutaneously, at 20 minutes: free HCl, 70; total acidity, 76 cc. of $\frac{1}{10}$ N HCl. These findings were essentially the same for samples of gastric juice on 8 successive days after the subcutaneous injection of histamin.

Course. During the patient's stay in the hospital clinical improvement took place after the first administration of liver and was followed by a gradual diminution of the number of loose stools and an increase of strength. On the day of discharge the blood count had reached only 2,015,000, with a hemoglobin of 56 per cent (Sahli), despite almost a month of therapy with potent extract derived from 800 to 900 gm. of liver daily.

CASE 41.—W. J., aged 41 years, white, male, an American salesman. Diagnosis: Dermoid cyst; chronic diarrhea; intestinal anastomoses; pernicious anemia. Admitted, March 30, 1930. Discharged, May 29, 1930.

Pertinent History. Nine years ago the patient was operated upon for a supposed retroperitoneal malignant condition at another clinic. He then received repeated Roentgen ray therapy, and several months later developed a fecal fistula into the sigmoid, from which, later, the discharge of a quantity of putty-like material together with hair led to a diagnosis of dermoid cyst as the original tumor. He then developed a second fistula into the small bowel, and during the next 4 years underwent 12 operations, by which numerous anastomoses and resections of the large bowel were performed. For the past 5 years he had suffered from varying degrees of ill health, exhibiting secondary anemia, marked loss of weight and a persistent watery diarrhea, requiring opium to keep the number of bowel movements as few as four or five daily. Beginning 2 years ago, and at intervals since, he had a sore tongue and transient paresthesia of the hands and feet. One year ago a blood examination showed: R. b. c., 2,000,000; hemoglobin, 60 per cent (Talqvist); color index, 1.5. Six months ago he was sicker and more anemic, but a diagnosis of pernicious anemia was rejected because the gastric analysis showed much free hydrochloric acid. However, at this time, on his own responsibility, he took liver extract for 2 weeks; he at once improved subjectively, and a few weeks later showed a higher blood count. He then discontinued liver extract, and in the 5 months before entry his symptoms increased and he took to his bed with persistent diarrhea, sore tongue and slight jaundice.

Admission Examination. The patient was pale, emaciated and had a slight jaundice of the scleræ and skin. The tongue appeared normal. The heart and lungs were essentially negative. The blood pressure was 85 systolic and 45 diastolic. The abdominal wall was very thin, showing peristalsis. There were many scars over the abdomen and a small fecal fistula in the left upper quadrant. The liver, spleen and kidneys were not felt. There was bilateral hydrocele. Slight pitting edema of both feet was observed. The reflexes and sensation were normal.

Laboratory Report. Urine: Clear, yellow, acid; specific gravity, 1.016; albumin, slightest possible trace; sugar, none; sediment, negative. *Stools:* Fermentative and watery; very acid; no gross blood; considerable mucus; occult blood test, moderately positive. *Blood:* R. b. c., 910,000; hemoglobin, 35 per cent (Sahli); color index, 1.9. W. b. c., 5350. The red cells were well filled with hemoglobin, showed much variation in size and shape and definite oval macrocytes. No abnormal white cells were seen. The platelets were somewhat diminished. *Gastric analysis:* Fasting contents not obtained. After 50 cc. of 7 per cent alcohol, at 20 minutes: free HCl, 0; total acidity, 6; at 40 minutes: free HCl, 0; total acidity, 7. After 0.5 mg. of histamin subcutaneously, at 20 minutes: free HCl, 52; total acidity, 71; at 40 minutes: free HCl, 83; total acidity, 89 cc. of $\frac{1}{10}$ N HCl per 100 cc.

Course. The fasting gastric juice after histamin stimulation, which invariably contained much free hydrochloric acid, was recovered each day for several days and utilized in the observations carried out on Case 42. During this initial period of 10 days the patient received 200 gm. of beef muscle daily without evidence of clinical improvement. Immediately thereafter the patient was given daily Liver

Extract No. 343 (N. N. R.), derived from 300 gm. of liver. He showed prompt improvement clinically and by the reticulocyte response, as shown in Table 1. At the end of a month his blood showed: R. b. c., 1,940,000; hemoglobin, 48 per cent (Sahli); at the end of 2 months: r. b. c., 3,020,000; hemoglobin, 65 per cent (Sahli); at 3 months: r. b. c., 3,940,000; hemoglobin, 65 per cent (Sahli); at 4 months: r. b. c., 4,710,000; hemoglobin, 70 per cent (Sahli). The clinical improvement was commensurate: the diarrhea was less; the patient felt stronger, ate well and gained much weight.

Case A.—C. D., aged 42 years, female, white, single, American. Diagnosis: Secondary anemia; hepatic enlargement. Admitted, February 3, 1930. Discharged, May 18, 1930.

Pertinent History. The patient was always well until about 5 years ago, when all her teeth were extracted because of mild rheumatic attacks. One year ago she began to lose weight and to become pale. At this time she noticed a tightness in the epigastrium coming on immediately after meals. After the teeth were extracted her diet became extremely limited. She ordinarily ate no breakfast; took crackers, toast and tea for lunch and for supper, and sometimes corned beef and cabbage at lunch or supper. She never observed any blood loss during this time.

Admission Examination. The patient was fairly well nourished. Her skin had a waxy pallor; the mucous membranes were very pale and without petechiæ. There was an iridectomy scar and external strabismus of the left eye. The vessels of the fundus were tortuous. All the teeth were replaced by a plate. The tongue showed a marked papillary atrophy. The lungs were clear. The heart was enlarged to left and right; the sounds were rapid, loud and forceful, with an increased aortic second sound and a systolic murmur over the precordium and axilla. The blood pressure was 110 systolic and 70 diastolic. The radial and brachial arteries were slightly thickened. The abdomen was slightly distended and a nontender mass with a smooth edge was felt at the level of the umbilicus in the right flank. The spleen was just palpable. There were large thrombosed bleeding hemorrhoids. There was some pitting edema of the ankles. The reflexes and sensation were normal.

Laboratory Reports. Urine: Cloudy, straw-colored, acid; specific gravity, 1.012; albumin, slight trace; sugar, none; sediment, 2 to 3 white blood cells per high-power field. *Stool:* Dark brown, formed; no gross blood or mucus. *Blood:* R. b. c., 1,280,000; hemoglobin, 9 per cent (Sahli); color index, 0.35. W. b. c., 3225. Differential: Polymorphonuclears, 80; lymphocytes, 10; mononuclears, 10 per cent. The red cells showed marked achromia and poikilocytosis. The platelets were somewhat reduced. The blood Wassermann was negative. *Gastric analysis:* Fasting contents: 5 cc. of clear, mucoid material; free HCl, 0; total acidity, 4. After 0.4 mg. of histamin subcutaneously, at 20 minutes: free HCl, 0; total acidity, 10 cc. of $\frac{1}{10}$ N HCl per 100 cc. *Roentgen rays:* Bones showed no evidence of metastases. Kidneys apparently of normal size. Barium enema showed no gross abnormality. A large, soft tissue tumor, presumably liver, displaced the cecum and hepatic flexure toward the midline.

Course. The patient made striking improvement clinically on daily doses of iron ammonium citrate varying from 1 to 6 gm. At the end of a month on 1 gm. of iron ammonium citrate daily the blood examination showed: R. b. c., 2,795,000; hemoglobin, 36 per cent (Sahli); at the end of 2 succeeding months, on 6 gm.: r. b. c., 4,850,000; hemoglobin, 84 per cent (Sahli). During the early part of this therapy gastric juice was removed from the patient daily for 10 days and used in the observations made on Case 44.

Case B.—H. R., aged 53 years, female, white, married, an Irish housewife. Diagnosis: Colitis; secondary anemia. Admitted, April 10, 1930. Discharged, July 14, 1930.

Pertinent History. The patient's health had usually been good except for a long-standing nonproductive cough. Four years ago she began to diet for obesity, reducing a fairly normal diet to tea, bread, occasionally lettuce and an egg or a little meat. One year ago she began to notice clots of blood in the stools. Four months ago she was much weaker and was told she looked pale. She became somewhat dyspneic on exertion and noticed a slight swelling of the ankles at night. The last menstrual period was a year ago. She lost 12 pounds in 4 years.

Admission Examination. The patient was a gray-haired, obese, rather sallow woman with distinctly pale skin and mucous membranes. There were faded purpuric spots on the right ankle. The tongue was almost completely devoid of papillæ. There was an upper plate and only a few lower teeth. The lungs were normal. The heart was somewhat enlarged to the left, with a soft systolic murmur at the apex. The blood pressure was 130 systolic and 80 diastolic. The abdomen was pendulous. There were small external hemorrhoids, not bleeding. There was a slight pitting edema of the ankles. There was no evidence of any neurologic disturbance.

Laboratory Reports. Urine: Faint trace of albumin; sediment; 5 to 9 w. b. c. per high-power field. *Stool:* Brown, unformed; no gross blood or mucus; negative for occult blood. *Nonprotein nitrogen:* 31.6 mg. per 100 cc. *Blood:* R. b. c.,

3,050,000; hemoglobin, 38 per cent (Sahli); color index, 0.62. W. b. c., 4150. Differential: Polymorphonuclears, 67; lymphocytes, 21; mononuclears, 9; eosinophils, 2; basophils, 1 per cent. The red cells showed marked achromia, anisocytosis and poikilocytosis. There were no abnormal white cells. The platelets were normal. The Kahn test was negative. *Gastric analysis:* Fasting contents: 45 cc. of cloudy, yellow fluid; free HCl, 0; total acidity, 13. After 0.5 mg. of histamin injected subcutaneously, at 30 minutes: free HCl, 0; total acidity, 15 cc. of $\frac{1}{10}$ N HCl. *Roentgen rays:* Gastrointestinal tract showed a normal esophagus, stomach and duodenal cap, but evidence of external pressure from the gall bladder and delay in the second position of the duodenum. Marked hyperperistalsis was noted throughout the bowel. A barium enema showed complete absence of haustration in the transverse colon and general irritation. Proctoscopy showed a small ulcer within the rectum.

Course. Beginning 3 days after entry the gastric juice of this patient was collected daily for 10 days and used in the observations on Case 45. The patient was then given small doses of iron which showed no effect on blood formation within 10 days. Later, she was given iron in large dosage and gradually recovered from her anemia.

CASE C.—L. G., aged 53 years, male, white, a single Portuguese stationary engineer. Diagnosis: Subacute combined degeneration of the spinal cord; hypertrophic arthritis of the spine. Admitted, April 25, 1930. Discharged, November 17, 1930.

Pertinent History. Aside from minor traumatic injuries the patient was well until the present illness. He worked as a fireman until 9 years ago, since then as an engineer. His diet had always contained meat, fruit and vegetables; he had never used alcohol or drugs. His appetite had always been excellent; his bowels fairly regular. On rare occasions he had vomited a little after a hearty breakfast. A month ago, after an unusual exposure to moisture while at work, he noticed pain in the left elbow radiating to the left shoulder and chest, especially on motion. Two days later both legs became weak, and he had a feeling as of pins and needles in the soles of his feet. He had no chills or fever.

Admission Examination. The patient was well developed and nourished, with good color. The tongue was normal. Aside from very bad teeth and enlarged inguinal glands, all positive findings were related to the neurologic examination. The optic disks were slightly pale. The strength of the arms was normal. All muscle groups of the left leg were weaker than those of the right. The arm reflexes were hyperactive. All abdominal reflexes were absent. The ankle and knee reflexes were hyperactive, with a well-sustained ankle clonus on the left and a few jerks on the right. Bilateral positive Babinski reactions were obtained. Position sense of the toes was absent. The vibration sense was absent on the left tibia and much impaired on the right. The gait was slow and spastic. The patient was mentally normal, but poorly educated.

Laboratory Reports. Urine: Negative. *Blood:* R. b. c., 5,360,000; hemoglobin, 90 per cent (Sahli). W. b. c., 7300. Differential: Polymorphonuclears, 80; lymphocytes, 14; mononuclears, 3; eosinophils, 1; basophils, 2 per cent. The red cells were normal in size and shape and normally filled with hemoglobin. There were no abnormal white cells. The platelets were normal. The blood Wassermann was negative. *Gastric analysis:* Fasting contents: free HCl, 0; total acidity, 14 cc. of $\frac{1}{10}$ N HCl per 100 cc. After 50 cc. of 10 per cent alcohol, at 15 minutes: free HCl, 0; total acidity, 3; at 30 minutes: free HCl, 0; total acidity, 9. After the subcutaneous injection of 0.8 mg. of histamin, at 15 minutes: free HCl, 0; total acidity, 11; at 30 minutes: free HCl, 0. *Lumbar puncture:* Normal dynamics and pressure. Spinal fluid, clear, colorless, cell-free. Globulin test, negative. Total protein, 37 mg. per 100 cc. Wassermann, negative. Colloidal-gold curve, 0000000000. *Roentgen ray:* Dorsal spine showed extensive hypertrophic arthritis. Cervical spine, negative.

Course. The gastric juice of this patient was removed daily after the subcutaneous injection of histamin and used in the observations made on Case 46. Subsequently the patient made considerable improvement under treatment with vitamin B and raw liver.

CASE D.—A. L., aged 28 years, female, white, a single American. Diagnosis: Chlorotic anemia of pregnancy. Admitted, September 29, 1930. Discharged, October 27, 1930.

Pertinent History. The patient was always healthy until she became pregnant, 9 months before admission. She had always been somewhat pale and had a sister who became anemic during pregnancy. During the gestation period the patient became increasingly pale. She became somewhat short of breath on exertion during the latter months and had some edema of the ankles just before delivery. She maintained a good appetite, and ate as usual a diet consisting mainly of starches with rarely vegetables and meat. She was somewhat constipated. She had no sore tongue, paresthesia, loss of blood or urinary symptoms. She was delivered of a normal male child 3 days before entry without unusual loss of blood.

Admission Examination. The patient was moderately well nourished; the skin and mucous membranes were very pale. There was evidence of much dental work. The tongue was extremely smooth and atrophic. The rest of the examination was

negative except for a soft blowing systolic murmur over the apex of the heart. The reflexes were normal.

Laboratory Reports. Urine: Negative. *Stools:* Negative. *Blood:* R. b. c., 3,325,000; hemoglobin, 36 per cent (Sahli); color index, 0.54. W. b. c., 11,450. Differential: Polymorphonuclears, 76; lymphocytes, 18; mononuclears, 4; eosinophils, 2 per cent. The red blood cells varied in size and shape and were markedly achromic. The platelets were increased. The blood Wassermann was negative. *Gastric analysis:* Fasting contents: 25 cc. of fluid: free HCl, 0; total acidity, 13. After 50 cc. of 7 per cent alcohol, at 20 minutes: free HCl, 0; total acidity, 7. After 0.8 mg. histamin, at 15 minutes: free HCl, 0; total acidity, 7; at 30 minutes: free HCl, 0; total acidity, 5 cc. of $\frac{1}{10}$ N HCl per 100 cc.

Course. During a period of 10 days gastric juice was daily removed after histamin stimulation for use in the observations made on Case 47. The patient was then given iron ammonium citrate in 6-gm. daily doses, which resulted in a prompt reticulocyte response and increase of red blood cells followed by rapid clinical improvement.

Summary and Conclusions. 1. Certain apparent exceptions to the hypothesis that pernicious anemia is produced by an inadequate gastric digestion of protein, thus causing a virtual deficiency in the presence of a normal diet, have been examined and found to offer no exception to the theory.

2. The experiments given below confirm the negative evidence of those of the three preceding papers of this series, and demonstrate positively that the existing tests for hydrochloric acid, pepsin and rennin of the gastric juice are not necessarily related to the presence or absence of the intrinsic factor of normal human gastric juice essential to the reaction with beef muscle described in these papers since:

A. *The intrinsic factor was absent from the otherwise normal gastric contents of 2 cases of pernicious anemia in relapse.*

(1) To each of 2 patients with the blood picture of pernicious anemia, but with an apparently normal gastric contents, beef muscle was given daily for 10 days without effect on blood formation.

(2) The fasting gastric juice of each of these 2 patients, secreted after histamin injection, was incubated daily with beef muscle and the resulting material given respectively to 2 typical cases of Addisonian pernicious anemia without effect on blood formation in either case within 10 days.

(3) Each of the 2 patients whose gastric juice was thus found to have no specific effect on beef muscle subsequently reacted positively to comparable doses of liver or liver extract by mouth.

B. *The intrinsic factor was present in the otherwise achylic gastric contents of a patient without anemia and of 3 patients with hypochromic anemia.*

(1) The gastric juice of a patient with no evidence of any disturbance of blood formation, and the gastric juice of each of 3 patients with hypochromic anemia were found even after histamin stimulation to contain no free hydrochloric acid and little or none of the common enzymes of the normal stomach.

(2) The fasting gastric juice of each of these 4 patients, secreted after histamin stimulation, was incubated daily with beef muscle and the resulting material administered respectively to 4 typical cases of Addisonian pernicious anemia with positive effects on blood formation in each case within 10 days.

3. In 1 of the cases of pernicious anemia with an apparently normal gastric juice, the intrinsic factor shown to have been absent in relapse was found to be present after the remission induced by liver extract.

4. The facts concerning the extrinsic and intrinsic factors and their relationship to their hematopoietic product described in this and our previous papers have been considered in relation to the age incidence of the disease and the tendency to spontaneous fluctuations of the blood count formerly noted.

5. Evidence for an accessory rôle in the etiology of pernicious anemia of a difficulty with the absorption of hematopoietic substance at least in certain cases of the disease is presented.

NOTE.—We are greatly indebted to Dr. George P. Robb for his assistance in carrying out certain of the observations reported in this paper. We wish to express our thanks to Miss Margaret Evans and Miss Charlotte Nicklin for the technical studies of the blood.

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HODGKIN'S DISEASE OF BONE MARROW AND SPLEEN WITHOUT APPARENT INVOLVEMENT OF LYMPH NODES.*

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In Hodgkin's[1] original article, "Morbid Appearances of the Absorbent Glands and the Spleen," which was published in 1832, 7 cases were described which all showed splenic and lymphoid enlargement. Today, to be sure, they would not be all recognized as true Hodgkin's disease. There was naturally no mention made of the bone marrow by Hodgkin's paper, as this tissue was not an object even of gross study until after Neumann's studies some 40 years later. Ever since Hodgkin's time the lymph nodes and the spleen have been considered the chief organs to be involved in Hodgkin's disease as we know it today, though various atypical pathologic types have been emphasized depending on the greater prominence of one or other group of involved organs. Thus "splenic Hodgkin's disease" is spoken of when the primary or most marked lesion occurs in this organ. In abdominal Hodgkin's granuloma the mesenteric or retroperitoneal nodes show the most prominent lesions (in a few cases that we have seen massive involvement of these nodes was accompanied by little or no change else-

* Read before the Philadelphia Pathological Society, May 14, 1931.

where); in the rarer gastrointestinal form the lesions may be almost entirely restricted to the mucosa and adjacent lymph nodes. Bone marrow lesions are not uncommonly found histologically (30 to 40 per cent, Ziegler;[2] 50 per cent, Symmers[3]), as one would expect in a disease chiefly involving the hemolytopoietic system. Cutaneous involvement is far from rare and the characteristic lesions also have been found in many other organs, such as the bones, "thyroid, pancreas, adrenal, heart and voluntary muscles, esophagus, breast, tonsils, ovary" (Ewing[4]). A typical case in the uterus has also been described. Dr. Strumia is reporting tonight such a case of unusually wide distribution. The commonest type, however, still remains that in which the several chains of superficial lymph nodes are involved, usually the cervical, axillary, inguinal, etc., though even here Ewing[4] and Symmers[3] consider that these may be the superficial manifestation of a primary internal involvement.

As far as I have been able to find, however, there has been no case reported in which the involvement was chiefly of the spleen and bone marrow, and where no lymph node involvement could be found. In Symmers',[5] Dowd's[6] and Wade's[7] cases of the splenic type no superficial lymph nodes were found involved, or abdominal nodes at operation, but these cases did not come to autopsy. As the present case has already been referred to by Rolleston,[8] in his Schorstein Lecture on Hodgkin's disease, and as it must be of considerable rarity, it seems desirable to put it on public record. It is, of course, impossible entirely to rule out all lymph node involvement in this case, though especially careful search was made at the time of autopsy. As Fraenkel[9] well notes, "It may happen that the majority of the lymph nodes seen macroscopically and microscopically have seemed to have been spared and that only in one spot may a small lymph node be involved. In a case of the author's this occurred in the supraclavicular fossa." It is obvious that in order completely to rule out lymph node involvement this would necessitate serial section of all lymph nodes of the body – an impossible task. Short of this we can only state that a very careful examination failed to reveal any involvement of lymph nodes and that the bone marrow and splenic lesions were undoubtedly of prime importance and that one or the other was in all probability the primary site. The absence in this case of lymph node material for histologic study is regrettable, but, on theoretical grounds at least, there is the consolation that even completely negative results in several nodes would not meet the objection above referred to. An excellent review of the whole subject of Hodgkin's disease has recently been published by Simonds.[10]

Case Report. M. D. (1925—242), a white male, aged 55 years, was admitted to the medical ward (service of Dr. Boston) of the Philadelphia General Hospital on November 25, 1924, complaining of weakness in the legs.

The patient, a painter by occupation, lately has noticed weakness in his

legs upon ascending stairs. He has been short of breath for about 6 months; at present when he attempts to go upstairs he gets short of breath, dizzy, and his heart begins to beat very fast. He has profuse nocturia, passing large quantities of urine, from 2 to 3 quarts a night. His appetite has been poor and bowels constipated, with periods of diarrhea. He lost 15 pounds in the last month and has had numbness, weakness and cramps in his legs and arms.

Past History. He had scarlet fever when a child, and has had pneumonia.

Social History. A painter all his life, he has never had colic. He had gonorrhea in boyhood; denies chancre; has been a moderate drinker of alcohol. His family history is negative; no familial tendencies.

Physical Examination. The patient is an elderly white adult male, lying comfortably in bed. The skin is generally a pallid, yellow color; there is no edema, cyanosis or dyspnea. The eyes, ears and nose are negative. There is facial weakness on the left side, and the tongue deviates to the left with a coarse tremor. The teeth are carious. Neck: Venous pulsations are seen on both sides; there are no palpable lymph nodes. Chest: The breath sounds are easily heard and apparently normal. The heart is negative. The pulse is accelerated but regular; it is small in volume. The blood pressure is 120 systolic and 50 diastolic. The abdomen is prominent in the upper half, with muscle spasm over these parts. The lower edge of the liver reaches the level of the umbilicus. The spleen extends to the level of the anterior superior spine. The extremities are negative.

Laboratory Tests. Urine: Heavy trace of albumin. Specific gravity, 1010. Hyalin and granular casts, red and white blood cells, few in number. Negative for urobilin. *Blood:* The Wassermann test is negative with both antigens. Blood chemistry: nonprotein nitrogen, 60 mg.; uric acid, 7 mg.; creatinin, 2 mg.; sugar, 150 mg. Hemolysis: begins at 0.46 per cent NaCl; is complete at 0.32. The platelets number 186,000 per c.mm. The blood serum is negative for the van den Bergh reaction. On admission the erythrocytes numbered 1,070,000 per c.mm., with anisocytosis, poikilocytosis and polychromatophilia; leukocytes, 8200 (78 per cent polymorphonuclears, 19 per cent lymphocytes). February 5, 1925: Erythrocytes, 1,116,000; leukocytes, 3700 (54 per cent polymorphonuclears, 43 per cent lymphocytes). Hemoglobin, 4.4 gm. No stippling. *Feces:* Urobilin, 1600 units (Addis).

Progress. The patient was transfused several times but gradually weakened and died on March 24, 1925.

Autopsy Abstract. Autopsy (9679, 1925—242) was performed by Dr. Palomeque 6 hours after death. The body weighs 125 pounds and is 170 cm. long, well developed and well nourished. There is marked pallor of the skin and mucous membranes. The gums are devoid of teeth. The neck is somewhat muscular and shows no palpable glands on careful examination. The thyroid is normal, the chest wall barrel shaped. The abdomen, large and protuberant, with definite fullness along the left external aspect and in the right superior quadrant. The lower half is distended. The thighs show normal muscular development but are very flabby, with moderate edema of the ankles. There are no lymph node enlargements in the axilla, groin, popliteal or other spaces.

Internal Organs. A substantial layer of fat of the abdominal wall measures 4 cm. in depth. There are about 3500 cc. of light, straw-colored fluid in the peritoneal cavity. No abnormal lymph nodes are found in the mediastinum, mesentery or retroperitoneum. There are about 1000 cc. of pale clear straw-colored fluid in the left pleural cavity and 1200 in the right. The pericardium is markedly distended and contains about 500 cc. of slightly turbid fluid.

Spleen. The spleen occupies the whole left side of the abdomen, extending to the anterior axillary line and down to the anterior superior spine of

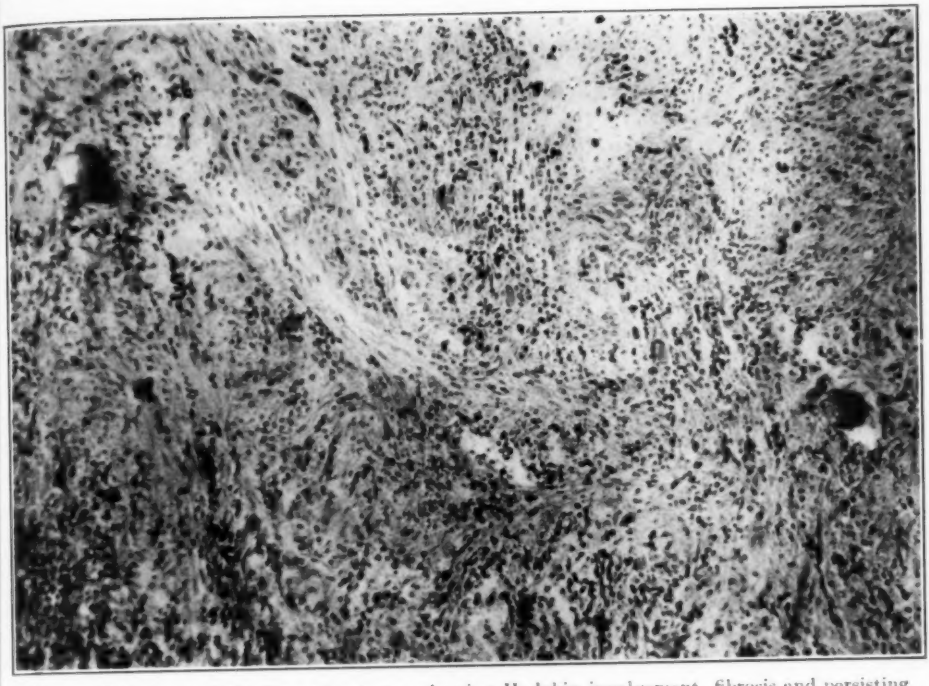

FIG. 1.—Histology of the femoral marrow, showing Hodgkin involvement, fibrosis and persisting hemolytopoiesis. (× 100.)

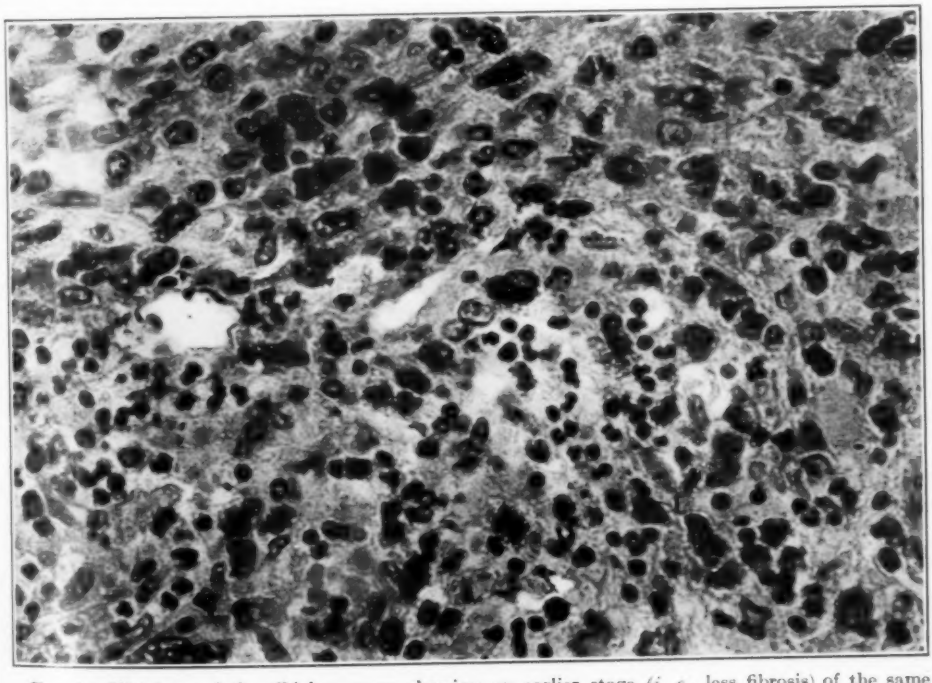

FIG. 2.—Histology of the tibial marrow, showing an earlier stage (*i. e.*, less fibrosis) of the same picture—endothelioid, Dorothy Reed cells, lymphocytes, polymorphonuclears, etc. The eosinophilic myelocytes can be made out on close inspection. (× 560.)

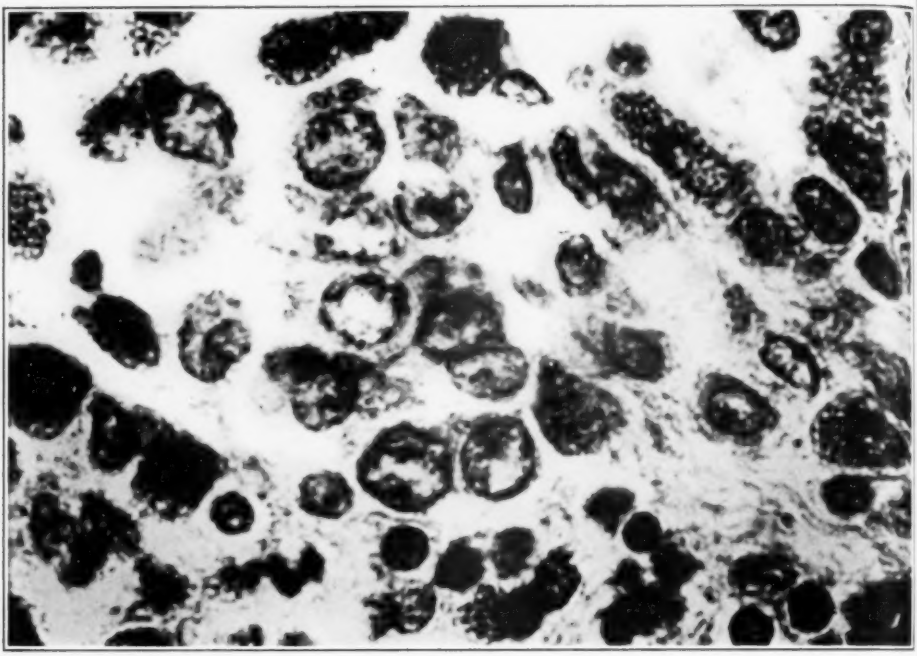

FIG. 3.—The same high power. The coarse granules of a dozen or more eosinophilic myelocytes can easily be distinguished. (× 1400.)

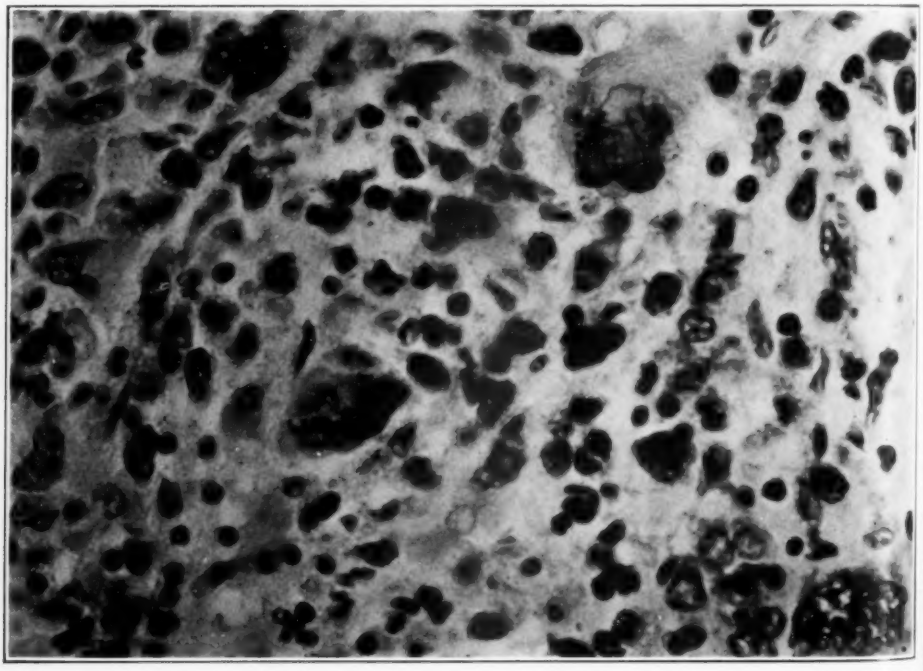

FIG. 4.—Histology of the splenic pulp, showing its great cellularity; lymphocytes; endothelioid and Dorothy Reed cells and eosinophilic myelocytes are numerous. (× 840.)

the ileum. It weighs 1090 gm. and measures 22 by 16 by 7 cm. It is of triangular shape, showing distinct lobulations. The capsule is grayish-white and tensely stretched on the splenic tissue and without thickenings or adhesions. The organ cuts with increased resistance, showing a homogeneous pinkish-red color, smooth and glistening and very firm. The lymphatic follicles are not visible. A few trabeculæ can be made out. There is no congestion and no blood is scraped from its surface. The splenic artery is sclerosed, of normal caliber, patent throughout. The splenic vein is somewhat larger than the artery and slightly sclerosed.

Heart. The heart is large, weighing 500 gm. There is definite hypertrophy of the right side with moderate fatty infiltration. On the left side there is moderate fibrosis of the musculature. The valves are of apparently normal size and show no marked lesions. The coronary vessels show only slight sclerosis, as does the aorta.

Lungs. The lungs show nothing noteworthy beyond slight emphysema.

Adrenals. The adrenals are apparently normal.

Kidneys. The kidneys weigh 200 and 220 gm. respectively, and are reddish-brown and firm. The capsule strips with slight difficulty, showing a granular surface which cuts with difficulty. The striations are obscured. The pyramids are pale and firm. The bloodvessels show moderate sclerosis. There is one large urinary retention cyst, 15 mm. in diameter, on the left kidney. Chronic arteriolar nephrosclerosis.

Liver. The liver weighs 2190 gm., appears very large, brown in color and fairly firm with rounded edges. It cuts with increased resistance, the cut surface being smooth and glistening, and shows numerous small whitish areas. There is an increase of fibrous tissue and a moderate congestion. Moderate cirrhosis.

Gall Bladder and Pancreas. Normal. The pancreatic artery is sclerotic.

Vena Cava and Portal Veins. Negative.

Digestive Tract. The *esophagus* is normal.

Stomach. Normal with smooth and glistening mucous membrane. No lesions found.

Duodenum, Jejunum, Ileum and Colon. Apparently negative, except for some congestion.

Genito-urinary Tract. No gross lesions.

Prostate. Small and atrophic.

Seminal Vesicles. Apparently normal.

Bone Marrow. The middle third of the right femur shows the marrow pinkish-red in color and hyperplastic. The marrow of the upper third of the right tibia shows a distinct hyperplasia, the medullary canal, containing flabby, pinkish-red marrow with a decreased amount of fat.

Brain. Is very pale and shows slight atrophy of convex surface and slight arteriosclerosis.

Histologic Examination. Examination of heart, lung, kidneys, esophagus, stomach, duodenum, pancreas and adrenal confirm the picture given in the gross inspection. In none of the lymphoid collections of the mucosæ were any abnormalities found. The lung shows in addition to the emphysema some carbon and "heart failure" cells but nothing resembling Hodgkin's infiltrations.

The *liver* (of which an extremely small piece was taken for section) does not include any of the whitish nodules mentioned. It shows slight thickening of the capsule, general slight diffuse increase of loose fibrous tissue, congestion and atrophy of the liver cords, with deposition within the liver cells of granules of brownish pigment. In some areas the liver cells have an indefinite outline and take a paler acid stain, as if degenerated. A few large mononuclear and multinuclear cells are found in the sinuses, that are of the Hodgkin type.

Spleen. The capsule is thickened and shows spots of adhesions. The pulp shows a scarcity of Malpighian follicles, which are small and without so-called "germinal centers." Immediately beneath the capsule (to the depth of 1 low power field) it is definitely poorer in cells than deeper in. In the deeper areas it presents a fairly homogeneous appearance, due to a variety of cells scattered through a matrix of slightly but definitely increased delicate fibrous tissue. The small sinuses can thus be more easily identified, and are closely lined with cuboidal (not flattened) endothelial cells. In the pulp the most striking cells are eosinophilic myelocytes scattered diffusely, but in some areas composing more than half of the cells found. They are even found in small numbers in the follicles. Next most prominent (and probably more numerous) are the pleomorphic large Hodgkin cells, varying much in size, with pale to dark staining nuclei, and with chromatin both clumped and finely divided in different cells. The long thin varieties have the paler nuclei and their appearance merges with that of fibroblasts. The round, dark-staining varieties occasionally are multinucleated (Dorothy Reed cells); their nuclei vary from a vesicular type, with a few chromatin dots, to solid opaque chromatic masses (pyknotic, in the sense of condensation, but without reduction in amount of chromatin). Lymphocytes occur in moderate numbers; polymorphonuclears and hemosiderin are both rare. No other hemopoietic cells are recognized. In the subcapsular zone, the cells are much rarer, disclosing the fibrous framework and sinus outlines more clearly, also some erythrocytes in both sinuses and polyp. Blood-vessels and trabeculæ present little of note.

Bone Marrow. Femur: To the naked eye the section has the appearance of a solid tissue, such as lymph node. Under low magnification the marrow is seen to be entirely made up of hemolytopoietic cells and fibrous tissue. If it were not for an occasional bone spicule, it could not possibly be recognized as bone marrow. In the more cellular areas interspersed through a rather loose fibrous tissue are various cells, of which the most prominent are megakaryocytes, and the eosinophilic myelocytes and mononuclear and multinuclear "endothelioid" cells, like those described in the spleen. Neutrophilic myelocytes and various immature cells of the erythrocytic series occur in moderate numbers. One perivenal collection of lymphocytes suggests a lymphopoietic focus.

This appears to be a combination of an extensive but late (fibrous stage) Hodgkin involvement of the marrow with persisting hemopoiesis.

In the tibial marrow the cellularity is much greater and the fibrosing process much less advanced than in the femoral marrow. Except that erythrocytes and pigment bearing phagocytes are somewhat more common, no essential differences in the quality of the cells concerned can be found from those of the femoral marrow. The immature erythrocytic cells are somewhat less frequent and pyknotic nuclei more so.

Summary. 1. A fatal case of Hodgkin's disease with autopsy is reported that was practically limited to the spleen and bone marrow, though in these two organs the involvement was extensive. The histologic appearance of the femoral suggests that the disease process may have been primary in this tissue. Absolutely no lymph node involvement could be found and the lymphoid tissue of the gastro-intestinal tract was histologically unchanged.

2. While this does not constitute unequivocal proof of the absence of lymph node involvement, it points strongly in that direction; while the absence of lesions in the mucosæ and of the so-called germinal centers in the spleen suggest interesting speculations as

to the type of cell (reticular or endothelial) in which the disease process originates. It is suggested that the disease should be considered a disease of the hemolytopoietic or reticuloendothelial systems rather than of lymphoid tissue.

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CARDIAC PAIN AND SUDDEN DEATH.*

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In the lay mind, at least, cardiac pain is inseparably connected with sudden death; in fact, any form of heart disease is regarded as possessing that probability. It is only within recent years that the luxury of a sudden death has begun to be appreciated, and for centuries men have prayed to be delivered from this desirable ending.

There are two widespread fallacies regarding sudden unexpected death that are difficult to eradicate from the popular belief. The first, common to both laity and medical profession, is that most cases of sudden death are due to some form of apoplexy. Apoplexy does occur suddenly, but rare indeed is the death therefrom sudden. Rare cases of a pontine hemorrhage breaking into the fourth ventricle do occur, in which death is practically instantaneous, and rare also are those cases of rupture of small aneurysms on the circle of Willis which may cause actually sudden unexpected death. But the erroneous belief is widespread in the medical profession, and in the lay mind alike, that apoplexy is a frequent cause of sudden death.

* Presented before the Philadelphia County Medical Society, February 11, 1931.

The second fallacy, especially in the lay mind, is that any form of heart disease means the probability of sudden death. While it is true that the majority of instances of sudden unexpected death do occur in some forms of heart disease, yet statistics show unmistakably that the number of sudden deaths compared with the total number of deaths from cardiac diseases is really small.

In New York City, in 1924, 22 per cent of the total deaths were due to some form of heart disease, but only 4 per cent of these were recorded as due to acute endocarditis, acute myocarditis and angina pectoris, and only 2.5 per cent were due to angina alone. Ninety-one per cent of the deaths from acute endocarditis and myocarditis and 85 per cent from angina pectoris were reported through the Medical Examiner's office, indicating probably a sudden and unexpected death, or at least one unattended by medical care.

As is well known, however, in the chronic valvular diseases of the heart, and in the usual forms of chronic myocardial diseases, death comes in the vast majority of patients with the slow cardiac failure, and although death may be sudden, it is not unexpected.

During such infectious diseases as typhoid fever, yellow fever, smallpox and diphtheria, the acute intense myocardial degeneration may at times be the cause of sudden death.

Warthin has reported 8 cases of acute syphilitic myocarditis which were acute exacerbations of chronic syphilitic myocardial degeneration, in all of which the death was sudden, and in 3 of which it was both sudden and unexpected.

A frequent cause of sudden, unexpected death is a chronic fatty degeneration of the myocardium. Brouardel emphasizes the fact that these patients often look well, that they have but slight dyspnea and never any attacks with severe symptoms, or pains of anginal type, their physical examination reveals nothing and that they do not always have an undue amount of body fat. Brouardel has seen this condition in poorly nourished children; it also occurs in those who take excessive amounts of alcohol, with but little exercise.

In the myocardium there is infiltration of fat between the muscle fibers and a fatty degeneration of the myocardial fibers themselves, the yellow, brown, red faded leaf color of the soft heart wall is characteristic.

The cause of this suddenness of death in these patients is not clear. A possible suggestion may be ventured that, as in diphtheria, the atrioventricular bundle may be degenerated separately, or in conjunction with the contracting mass of the myocardium. Mönckeberg reports 21 cases of diphtheria in which the atrioventricular bundle was the seat of excessive fatty degeneration, in 5 of which the degeneration of the tissue was excessive. In only 1 of these cases did the myocardium show destruction equal to that of the atrioventricular bundle, and in only 6 instances did it show a fatty degeneration. In several instances the myocardium showed fibroid

degeneration, while the bundle showed severe fatty degeneration. The conducting system, therefore, of the heart in consequence of its partially independent blood supply can also be independently diseased. How frequently the lesions of the conducting system, independent of either the contracting myocardium, or the coronary system, produce sudden death, is as yet unknown.

Brouardel quotes Forbes as reporting that of 64 cases of angina, 49 (76.5 per cent) died suddenly. In those patients who survive one attack of angina, whether this symptom complex arises from coronary thrombosis, or is of aortic origin, with no occlusion of the coronary vessels, sudden death is not unexpected. Sudden and unexpected death in the first attack of aortic or noncoronary angina is not the usual occurrence. Wenckebach even reports that he has never seen such a death, but it is not a great rarity.

Both Kolisko and Brouardel record that sudden unexpected death occurs not infrequently from embolisms of the vessels of the heart, or thrombosis of the pulmonary artery, the emboli coming chiefly from varicose veins of the legs, or occurring postpartum or postabortum. Sudden death from such emboli may occur following abdominal or pelvic operations, and probably it is of sufficiently common occurrence to have occurred in the experience of most surgeons. Usually the patient has a warning feeling of sickness, dyspnea or cyanosis coming on suddenly, followed quickly by loss of consciousness and death. At times death is so sudden and unexpected that the patient seems to crumple up dead; at other times the clot lodges in a coronary artery, with death in a few hours, or after a longer period of time, as from primary thrombosis of the coronary arteries.

The statistics of Krumbhaar and Crowell present 654 cases of spontaneous rupture of the heart; 58.3 per cent occurred in males and 41.7 per cent in females; in 80 per cent of these cases it occurred in the left ventricle, in 10 per cent in the right ventricle, in 5 per cent in the right auricle and in only 2 per cent in the left auricle and in the interventricular septum with rupture of both ventricles simultaneously, or the exact site not definitely stated in 2 per cent. The long descending branch of the left coronary is most frequently thrombosed, usually producing an infarct near the apex and involving the septum. This occurred in 60 per cent of the cases, and in 23 per cent of the cases it was in the transverse branch of the left coronary supplying the posterior wall of the left ventricle, in which the thrombosis occurred. Spontaneous rupture of the heart is due in the great majority of cases to antecedent coronary disease, often with actual thrombosis and acute infarct, or subsequent degeneration of the muscle fibers with stretching of the thinned wall and final rupture with or without terminal necrosis of the fibers. These cardiac ruptures rarely occur before the age of 45 years, more often between the ages of 50 and 60 years, and in the greatest number of instances between the ages of 60 and 80 years.

It is interesting to note that in less than 25 per cent of 325 patients dying from rupture of the heart reported by Nuzum and Hagen was there any clinical suggestion of heart disease previous to the cardiac rupture. In the 75 per cent who gave no history of heart disease previous to the rupture the majority did not suffer both sudden and unexpected death. Where the death was not sudden, it did not occur for a few hours to two days after the beginning of the symptoms. Of 400 of the cases reported by Krumbhaar and Crowell, however, in 72 per cent the death was "sudden."

Thrombosis of the coronary artery without rupture of the heart is probably the most common cause of sudden and unexpected death.

Experimental ligation of the coronary arteries as well as blocking with lycopodium spores indicates that sudden death occurs when a sufficiently large area of myocardial tissue is deprived of its blood supply, death being caused by ventricular fibrillation.

The abundant anastomoses between the branches of the same coronary and between the right and left coronaries may at times protect the myocardium, even when large branches are suddenly occluded. When, however, the occlusion occurs at the origin of the coronary artery, due to atheromatous involvement at its origin in the aorta, sudden death may occur.

In bacterial endocarditis emboli at times go into the coronary arteries and cause sudden death; if the disease has been recognized death may be sudden, but not unexpected.

Excessive exertion or intense emotion may cause death suddenly, and often unexpectedly, in any excessive myocardial degeneration. Sexual intercouse produces one of the severest strains which a degenerated heart can suffer; sudden and unexpected death during coitus is a very common occurrence in aged men.

Tumors in the brain may be present and unsuspected, and specially gliomata may cause sudden and unexpected death through hemorrhage from rupture of their bloodvessels. Pachymeningitis hæmorrhagica may cause death, but it is a slow death like that from apoplexy.

In children tuberculous and other forms of meningitis may cause sudden and unexpected death before the disease has clearly manifested itself, and may be unrecognized. In diphtheria the sudden death is too familiar to be unexpected, and it may be caused either by laryngeal suffocation from edema of the glottis, or cardiac paralysis, for in cardiac paralysis the atrioventricular bundle is often diseased as well as the main contracting system of the myocardium.

The most unexpected and sudden death in apparently healthy children is a so-called thymic death. The child may turn white and die instantly, or be found dead when supposed to be taking a nap. The actual cause of this form of sudden death is unknown. One opinion is that death is caused by pressure on the heart and

trachea as the enlarged gland lies on the pulmonary artery and aorta, and covers the right auricle and two-thirds of the right ventricle. In the narrow opening of the thorax the pressure of the trachea and the larynx may cause spasm of the glottis, or pressure on the recurrent nerves may cause paralysis of the larynx. Timme's explanation of the cause of this form of death is that to overcome the effect of the characteristically small vessels, low blood sugar and consequent asthenia increased demands are put upon the adrenals. The thymus, pressing on the vagus and sympathetic plexuses about the base of the heart and great vessels, causes the maladjustment of the automatic regulatory control which enables the body to meet emergencies. Slight excess pressure on the vagus may stop the heart, and the adrenal system, which is pushed too much, cannot meet the emergency, and the heart stops beating and the patient dies.

Status lymphaticus produces a condition in which sudden unexpected death not infrequently occurs; this condition occurs most frequently between 20 and 40 years of age. In 5652 necropsies in Bellevue Hospital in New York, Symmers found 457 cases of this condition; of the 249 cases analyzed 118 were active, 89 were recessive and 42 were partial. The sudden unexpected deaths occurring at the onset of some infectious diseases as cerebrospinal meningitis and at the beginning of general anesthesia have been attributed to this condition. In status lymphaticus the rupture of the hypoplastic arteries, usually one of the basal arteries of the brain, has been in rare instances the cause of sudden and unexpected death.

Hemorrhages from the lungs of such volume as to cause sudden death are not uncommon; in New York City about 2 a month are reported to the Medical Examiner's office. These hemorrhages usually come from the walls of a tuberculous cavity.

Hemorrhages from the esophagus may also cause sudden death. These hemorrhages may be due to a cancerous growth of the esophagus eroding into the aorta, or to an aneurysm of the aorta eroding into esophagus.

Rarely, but more often than is usually clinically realized, in cirrhosis of the liver sudden fatal hemorrhage may occur from a rupture of the ring of varicose veins at the junction of the esophagus and stomach.

In the consideration, therefore, of sudden death we end where we began, that contrary to the beliefs of both the medical profession and the laity, sudden and unexpected death is but rarely produced by cerebral hemorrhage. The great majority of sudden unexpected deaths occur in certain forms of heart disease, but the overwhelming majority of deaths in heart disease are neither sudden nor unexpected.

In considering cardiac pain we must frankly admit that the explanations given for it, and the theories held concerning it are unsatisfactory, do not correspond with the experimental observa-

tions. Cardiac pain varies in its intensity from mild annoying precordial discomfort to the most intense forms of agony, spreading over various areas of the chest and arms. Clinically it almost invariably carries with it a sense of fear, because of the well-recognized belief that precordial pain means angina, and angina means sudden death.

Unquestionably the pain when it does occur arises from two different areas supplied by the coronary arteries, and their afferent nerves, one in the first portion of the aorta from the morbid conditions produced by aortitis, and the second is from the morbid conditions of the coronaries supplying the atrioventricular portion of the heart.

This difference in origin gives a different clinical picture to the type of pain. The aortic type corresponds to Heberden's first description, and, as you know, the pain is a substernal pain going up the chest into the throat, and at times into the jaw, and over the great occipital nerve, or else adding to or avoiding this area, going up to the left shoulder and down the left arm by the ulnar nerve to the tip of the fingers. It may, of course, begin substernally and go directly to the left arm or right arm, or both arms.

In this symptom complex there is also a tremendous viselike pressure from the muscles of the chest, there is often a curious conviction in consciousness that death is near and there is a noticeable lack of dyspnea, with normal steady pulse, and the patient gives one the picture of a stricken animal, not daring to move, sitting or standing in agony, waiting for death to relieve him, or turning with appealing eyes for relief. In the attacks of pain in the atrioventricular coronaries the pain in about one-third of the cases follows the same line up to the left shoulder, and down the arm, the patient complaining bitterly about both pain and dyspnea, but in about two-thirds of the cases the pain is felt in the epigastrium or in the lower part of the sternum, with a shooting pain around under the ribs in the sixth and seventh nerves. The patient often complains bitterly of the choking sensation from gas, and refuses to talk to you about the pain, disregards even the dyspnea, but discusses nothing but the indigestion and the oppressive gas from which he cannot obtain relief. The pain often is so intense in the epigastrium that the patient lies like one with acute perforation of the abdominal viscera, and the diagnosis between a coronary attack and gastric or duodenal perforation is often a difficult one. Often between attacks these patients with coronary disease suffer intense discomfort from the enormous amounts of gas that they discharge, either by mouth or by the bowel.

These patients with this coronary disease also have coronary thrombosis with its familiar picture, but what is not usually appreciated, they frequently have these attacks of pain without the thrombosis. These attacks of pain of both types are often brought

on by very slight exertion, or exposure to cold, or by some vigorous emotion. Often the most intense attacks occur in patients in their sleep, with seemingly the body at rest, and only the autonomic nervous system still active.

The anginal syndrome may follow an attack of acute infectious disease as influenza, and, curiously, the substernal pain radiating down the arm not uncommonly occurs with patients suffering from pernicious anemia, and it ceases immediately after blood transfusion. Intense precordial pain is very commonly complained of by those recovering from prolonged alcoholic intoxication.

Nicotin poisoning produces precordial pain very frequently in its minor degrees of intoxication. The use of tobacco by those subject to attacks of angina increases both the frequency and the intensity of the attacks.

Clinically the exhibition of the symptom complex of cardiac pain seems to arise in so many conditions as to baffle a comprehensive explanation. The pathologic anatomy found in those who have suffered from angina seems as incongruous as the clinical picture. Those who have the aortic pain show an aortitis very frequently of a luetic type, involving also the origin and a short distance into the coronary arteries, and they may also have arteriosclerosis of nonluetic causation of the coronary arteries. Those who have the coronary type of pain show arteriosclerotic changes in the coronaries and may have normal aortas, but many patients living and dying with aortitis and with sclerotic coronaries never show any cardiac pain whatever.

Obendorfer, Kirch and Edens, in recent excellent reviews, faced with the incongruity between pathologic anatomic and clinical manifestations of pain, conclude that spasm of the coronaries is the most probable explanation of the anginal symptoms. This is the belief usually accepted by the profession; others believe that it is the ischemia of the myocardium produced by the spasm, and not the spasm itself that produces the pain. Spasm of the coronary arteries is, however, a theoretical assumption and an unproven reality.

Others still believe that the myocardial muscle must be the cause of the pain, because angina occurs in those hearts which show myocardial degeneration, and yet hearts suffering from myocardial diseases are the ones most free from pain. Wenckebach believes that in some way there is a stasis in the coronary arteries whose distention produces pain, or that the depressor reflexes causing vasodilatation may be reversed into pressor reflexes causing vasoconstriction and a rise of blood pressure. Allbutt believed that anginal pain was due only to nerve endings in first portion of the aorta, that the coronary arteries had nothing to do with the pain but a great deal to do with the cause of death. Danielopolu believes that the metabolites of muscular action poison the heart

sufficiently to produce a cardiac failure and give pain. Pauli, in Vienna thinks it must be some lack of equilibrium between the two portions of the autonomic system. It is evident, therefore, that there is no definite agreement as to the cause of cardiac pain.

The operation of sympathectomy in recent years has helped to clarify the situation, in that it has shown that several different operations on the sympathetic and vagus systems have succeeded in stopping the attacks of pain, but no one operation has been always successful. It shows, therefore, that either different nerves vary greatly in different individuals in the transmission of their physiologic function, or else the breaking of the continuity of reflex action is equally effective as the cutting off of afferent sensory fibers and pathways.

The results of sympathectomy also indicate strongly the necessity of separating in ones clinical picture the pain of aortic origin from that of other coronary fields, since operations successful against the pain of aortic origin have failed in other patients when the pain arose from the atrioventricular coronaries. It has also become increasingly evident that in certain conditions in which the atrioventricular coronaries are involved sympathectomy not only is unsuccessful, but is distinctly contraindicated.

The morbid conditions found in aortitis in those giving a history of anginal pain are, according to Kutchera Aichbergen, that the adventitia of the aortic wall is adherent to the muscular media at the inflamed areas in the wall of the aorta, the wall being thinned at these points. The morphologic conditions for a sudden distention are, therefore, present, and the severest strain is to be expected exactly on the inflamed areas. It is in such cases as these that we find a previous history of angina pectoris, especially if the aortic valves are thickened or the coronary openings are narrowed or closed.

In aortitis the coronaries are often involved only near their mouths, or are entirely normal. It is difficult, therefore, to understand how the coronaries should be contracted in spasm, especially when they are protected from the thrust of the blood by either stenosis or by closure, and more especially still when their mouths are open by the fact that at each systole of the heart the coronary circulation is blocked by the contracting myocardium and the inflow only occurs during the relaxation of the diastolic period.

When there is much scar tissue, or calcified infiltration of the aortic wall, or in cases of large stiff walled aneurysm, the history of anginal pain is usually absent. Anginal pain occurs in thin walled mycotic aneurysms, and with ruptured aorta.

In arteriosclerosis of the bloodvessels, from whatever cause it arises, the first tissue to become involved is the internal elastic tissue. This breaks down, and is followed in the areas so affected by the thickening of the intima, which, according to Thoma, is a protective reaction in defence of the stretching muscularis.

Kutchera Aichbergen emphasizes the fact that with these thickened arteries, and with the calcified arteries, the anginal pains are less common, unless coronary thrombosis or coronary infarct has occurred. But with the distended walls frequently seen in the coronaries of those giving a history of angina pectoris all the tissues are thinned out and stretched, the muscularis is not hypertrophied as it would be from constant exercise of spasm and the internal elastic layer is often completely smoothed out, not normally folded like a neck ruff, and these changes can only be explained by the stretching of the internal elastic layer. It is this type of artery that is particularly prone to seizures of pain.

But after all, pathologic anatomy can only show how far at death the tissues had changed from normal, and perhaps what normal functions were inhibited during life. It often shows why certain symptoms occurred, or why at times the processes necessarily ended in death. It does not explain the functional reflexes which give rise to angina pectoris.

The more we study the clinical picture of angina pectoris and cardiac pain, the more are we forced to realize that the explanation lies in the normal anatomy of the vegetative nervous system, and in excessive function or perversion of the normal physiologic reflexes by which the heart and its own vascular system respond, or fail to respond, to the demands made upon them by the rest of the body through the circulation. In normal healthy athletic youth the heart responds instantly with unlimited power to all bodily demands, but as the hardiness of youth passes and bodily vigor declines, or sloth degenerates it, the heart loses its power for instant call, and although it may regain this power for a time through work and persistent repetition of its functions, there comes a time when senescence begins, when the heart and its vascular system are permanently damaged and it has lost its power to act and lost the ability to regain its former functional vigor. It is in this period of senescence in the fifties and sixties that angina usually occurs. Angina does not wait for the rigid calcified deposits of senility; it may well occur earlier. Syphilis demands its reckoning even in middle life, and Mönckeberg has shown that nonluetic arteriosclerosis of the coronaries frequently begins in early manhood, as youth is ended, and the descending branch of the left coronary is often the first artery in the body to be affected. Degenerative tissue, either cardiac or otherwise, cannot perform the vigorous functions of normal tissues, and either by failure to perform their functions, or through failure to prevent excesses, such as overdistention or stretching, excessive reflexes are set in motion. These produce the sensation of pain, and upset the smooth performance of the functions of other viscera, and we have the symptom of angina pectoris. Let us see now if the facts bear out this assumption, and if the normal anatomy and normal reflexes of the heart justify us in thinking in terms of the above statement.

All are familiar with the intricate anastomoses between the three sympathetic cardiac nerves in the neck and the three branches of the vagus going down to the cardiac plexus. Ransom has shown that above the middle ganglion of the sympathetic cord the afferent fibers carrying pain do not go. In the superior cardiac nerve go the pathways for transmission of the vasomotor reflexes. Arising from the aorta there is a nerve which usually has also a branch from the sympathetic system, and which goes up through the vagus and by a branch to the superior laryngeal nerve, or to its external branch. This is the depressor nerve which carries afferent impulses to the medulla, causing a lowering of blood pressure when the pressure becomes too high in the aorta, and it does this through stimulation of the dilator center, causing a general fall of blood pressure. The afferent nerves carrying pain from the heart and aorta go out through the inferior cardiac nerve, and the middle sympathetic nerve to the eighth cervical ganglion, and the first thoracic, or to the combined stellate ganglion, and also down to the five upper thoracic ganglia, going into the cord through the posterior roots of these spinal nerves.

There are also nerves in man, as shown by Braücke, Jonesco and Morehouse, going directly from the thoracic ganglia even as low as the seventh dorsal ganglion, without going through the main sympathetic cord up to the stellate ganglion, but which pass directly over to the lungs and the heart through the pulmonary and cardiac plexus. These carry accelerator fibers and also afferent fibers. The accelerator sympathetic fibers go up through the stellate ganglion from the upper thoracic nerves, and go through the inferior and middle cardiac nerves and from the loop of Vieussens to the heart. The afferent nerves coming from the heart pass out to the cord by the rami communicantes through the ganglions on the posterior nerve roots and in the cord they go up the spinothalamic tracts of the cord to the thalamus and thus ultimately reach the sphere of consciousness.

In the heart itself Woolhard has shown that the ordinary ganglia of the heart, which are so abundant around the great veins and on the auricles, belong to the vagal system, and are the ganglia which send out the postganglionic fibers of the vagal system. While the auricular and atrioventricular bundle are supplied by both systems, the ventricular muscles are apparently supplied by only the sympathetic nerves. The sympathetic fibers arise from the various ganglia in the main sympathetic trunk, and come to the heart as postganglionic fibers. Woolhard has also shown that on the main branches and arterioles of the coronary system the sympathetic fibers predominate, but the vagal fibers predominate on the arterioles and capillaries on the heart muscle. Anrep and his coworkers have brought forward strong evidence to show that the sympathetic nerves are the vasodilators of the coronary arteries and the vagus

nerves are the vasoconstrictors. It is important also to remember that the blood supply of the first portion of the aorta is only from both coronary arteries which form the vasæ vasorum of this portion of the aorta. The sensory nerves of the aorta and of the coronary arteries lie in the adventitia. The sensory nerves of the heart, therefore, lie in the adventitia of its bloodvessels, and to account for cardiac pain we must turn to some cause of nervous reaction to the nerve endings of these sensory nerves in the adventitia of the aorta and of the coronaries. Odermatt, in studying the sensitiveness of bloodvessels has clearly shown that some arteries are sensitive to ligation, small arteries more so than large ones, for example, the radial more so than the brachial, and he also, with Dogiel, proved that the sensory nerve endings of bloodvessels rested in their adventitial coat. Odermatt also found that arteries which were sensitive to ligation were also sensitive when their adventitia was stretched or distended, that is, stretching or distention of these same arteries produced pain. That it was by distention and not by contraction that pain arose. There is no evidence that arteries have colic in the same manner that intestines do.

Singer has demonstrated that an acute ischemia of the cardiac muscle is without any painful reaction in the experimental animal, and that the chemical and mechanical insults causing pain in the pericardium, epicardium, aorta and coronary vessels do not excite pain in the cardiac muscle. The pericardium is distinctly sensitive to mechanical and chemical irritation, but Faradic irritation provokes hardly any reaction. The epicardium is insensitive to electric, but sensitive to mechanical and especially to chemical irritation. The endocardium and the cardiac muscle were completely refractory to the above three forms of irritation. The sensibility of the coronary vessels is conditioned on the intactness of their adventitia. This portion of the aortic wall possesses a strong mechanical and chemical sensibility, but sensitiveness to pain on the part of the media and intima could not be demonstrated.

The aorta was but feebly sensitive to Faradic irritation. It is only mildly sensitive to chemical inflammatory irritations, but to mechanical irritation, such as pinching and pulling and stretching it was strongly sensitive. Here also the sensibility depends on the anatomic intactness of the aortic adventitia.

Spiegel and Wassermann have shown that at times stretching of the aorta produces pain, and that pain from the aorta follows the same pathways as pain from the heart. Jonesco and Singer have shown conclusively that only sympathetic fibers carry pain. There are no sensory fibers for pain in the parasympathetic nerves nor in the depressor nor in the vertebral nerves.

Singer showed that eradication of the stellate ganglion on the left side made the aorta and the left side of the heart insensitive, the right side of the heart was still slightly sensitive, the eradication

then of the right stellate ganglion made insensitive all cardiac and aortic tissues as far as the subclavian arteries.

Considering the coronary circulation, Anrep and his coworkers have found that the coronary outflow through the coronary sinus occurs in three waves—the first due to auricular contraction in presystole, the second, the smallest, is synchronous with the isometric period of ventricular rigidity, and the third, and largest, is synchronous with the ejection phase. During diastole the coronary outflow diminishes gradually, or very often abruptly, it may stop or continue. The minimum outflow, however, is always during the second half of diastole, unless the outflow is distorted by the auricular wave. With the closure of the aortic valves, the inflow begins and increases rapidly, then more slowly, and then increases constantly until the maximum of the inflow is reached, as systole begins. The coronary inflow diminishes rapidly during systole, reaching its minimum at the end of systole.

In the denervated heart aortic pressure is the only mechanical function determining coronary flow. In the denervated heart changes in the cardiac output and changes in the heart rate within wide limits and changes in strength of contraction have no direct influence on the coronary circulation, because the internal reflex mechanism is abolished.

According to Anrep and Segall, in the enervated heart, however, the coronary flow is extremely sensitive to changes in the output from the heart, although the arterial pressure still remains the chief factor influencing the coronary circulation.

The augmentation of the coronary flow and the acceleration of the heart, though simultaneous, are independent effects whether the heart is artificially stimulated to increase its rate or beats naturally with the Bainbridge reflex in play. This reflex being that an increased venous pressure on the nerve fibers in the right auricle restrains the vagus action and allows the accelerators to increase the heart rate. Anrep and Segall's coronary reflex is also of great importance, this reflex being that with an increased cardiac output, and, therefore, a greater performance of work by the heart there is an increase in the coronary blood flow. This reflex is abolished when the vagi are cut. The same rise of blood pressure produces a much greater increase in the coronary flow when the output of the heart is large than when it is small, thus reproducing the circulatory conditions in muscular exercise or in the condition of a simple increase in arterial blood pressure.

Anrep and Segall's experiments strongly indicate the existence of vasoconstrictor fibers in the parasympathetic nerves; these vasoconstrictor fibers are in a state of partial tonic excitation. This coronary reflex enables the heart to regulate its own blood supply, not only in proportion to an increase in the arterial resistance, but also proportionately to the venous filling of the ventricles. This

coronary reflex must play an important part in the circulatory conditions observed in muscular exercise, enabling the heart to adapt itself to increased demands while safeguarding its blood supply. Anrep further noted that a rise in cerebral blood pressure slightly diminished, and a fall increased the coronary flow.

Beginning with the reflexes occurring in the early stages of muscular exercise, since it is the sudden call to slight exertion as walking against the wind or up a slight grade which are often the earliest actions to inform a patient that his heart can give him pain. The first reflex at the beginning of exertion is probably that from the higher nervous centers which quickens and deepens the respiration.

This starts the necessary supply of increased oxygen, and with the bellows effect of the chest increases the venous flow into the heart. As the skeletal muscles contract, further increase of blood goes to the heart through the big veins, and there is a rise of capillary and venous pressure, and there occurs in the right auricle a vagal reflex on the nerves around the great veins as the increased blood distends the auricle; the vagus is reflexly depressed and the accelerators are stimulated so that the rate of the heart increases in proportion to the venous return, and the blood is hurried on through the heart. The increase of the CO_2 and lack of O_2 also accelerates the heart. The anoxemia also greatly increases the coronary flow. There is a simultaneous rapid rise in arterial pressure, and as the blood pours into the ventricles there is a stretching of the myocardial muscles, with an increased output per beat of the heart. Both this rise of aortic pressure and increased cardiac output equally increase the coronary flow through the action of Anrep's coronary reflex by the inhibition of the vagal vasoconstrictor fibers, producing capillary and arteriolar dilatation with increased coronary flow. The rise of the CO_2 tension and the H-ion concentration of the blood also adds to the increase of the coronary circulation. In normal vigorous cardiac contraction the coronary vessels are compressed and emptied; during each beat of the heart the coronary circulation varies between practically emptied vessels and well-filled flowing circulation. But with the breaking down of myocardial contraction from degeneration of the muscles, with increasing blood from exertion, and with the anoxemia increasing coronary flow, and the myocardial muscles stretching to increase their action to produce increased output, the degenerated muscles cannot sufficiently contract, and the heart is in the condition of dependence for its coronary blood supply on increase of blood pressure. The degenerated muscle cannot contract vigorously enough to empty out the heart nor its own coronaries, nor can the heart increase the vigor of its contraction. For a time its increased rate per minute may act as a substitute for increased output per beat, but there comes a time when with the incompetent cardiac muscle there occurs an increasing congestion and finally dilatation of the

coronaries by which stretching of the adventitia is produced from overdistention of the diseased arteries, and pain is the result. This pain comes from the coronary vessels, and pain occurs until the coronary circulation can recover itself, through increased muscular action of the myocardium, or diminished inflow of blood into the heart brings relief.

All these circulatory reflexes do not necessarily act when pain arises from the aorta. With an aortitis and diseased wall, as we have shown, where the adventitia and muscularis are adherent together, or the inflammatory conditions in the vasa vasorum of the adventitia cause morbid conditions to arise, which press on the sensory nerve endings, with the increase of blood pressure in the aorta, which emotion may cause, which increased exertion causes, then there is an increase of the stretching of the aorta sufficient to produce pain, but not sufficient to cause reflex actions of the depressor nerve to occur, and bring about a cessation of this stretching. The giving of nitrite of amyl instantly produces a relaxation of the muscularis, of all bloodvessels and a fall of blood pressure and the painful stretching ceases. The action of the nitrites is substituted for that of the depressor nerve.

Summarizing briefly, it is evident, therefore, that the sensory afferent nerves of the heart and aorta originate and run in the adventitia of the first portion of the aorta and of the coronary arteries and belong only to the sympathetic systems of the autonomic nervous system. Stretching and overdistention of these vessels is brought about by normal circulatory reflexes which in diseased tissues cause excessive stretching of the aorta before the depressor reflexes bring relief or by overfilling cause overdistention of arteriosclerotic walls of the coronary arteries. As long as the circulatory reflexes do not upset the equilibrium between the myocardium and its bloodvessels there is no pain. When, however, the afferent functions of the nerves are adequately disturbed, or the myocardium so degenerated that it cannot under reflex stimulation contract normally, the normal increased rise of blood pressure and the circulatory reflexes produce excessive dilatation of the diseased bloodvessels and pain results when the heart endeavors to answer the demands for increased work.

This theory also explains the various clinical exhibitions of pain in coronary infarcts and thrombosis; if they are in small vessels local overfilling proximal to the infarct of the coronary vessel is sufficient to give pain. This also can be the cause of pain in infarcts from large vessels, but there is also added when large infarcts occur the sudden diminution in contractile power in the myocardium, and there are present two causes for overdistention and stretching of the adventitia of the coronary vessels. Probably with the intense fall of blood pressure occurring with infarction the pain is chiefly due to the stretching of the adventitia of the coronary vessels at

the proximal side of the infarct. Pain will probably not occur even in cardiac infarct if there is by chance sufficient collateral circulation to draw off the blood and prevent the coronary distention.

This theory here offered accounts for the fact that in some operations of sympathectomy, even with none of the sensory fibers cut or disturbed, the attacks of pain may entirely cease when the continuity of reflex action is prevented, and the rise of blood pressure does not take place, and on exertion the adventitia of the aorta is not overstretched to give pain. In those odd cases of pernicious anemia in which the symptom complex of angina occurs, we start with an overdistention of the coronary vessels, because the anemia itself may augment as much as six times the normal amount of the average coronary flow. With an anoxemia the myocardium cannot normally contract, and there arises a failure of the myocardium producing the coronary stasis in diseased arteries. With a blood transfusion the anemia disappears, the anoxemia vanishes, the myocardial contracting power returns, the coronaries are not overdistended and the pain ceases.

In the poisoning by nicotin the action of the drug is at the synapses in the sympathetic ganglia, with the paralysis of the postganglionic fibers. This means that the accelerators are sufficiently poisoned to inhibit the contracting and conducting power of the ventricular muscle, for, as we have shown, the accelerators preside over these functions of the ventricle, and Woolhard has shown that the ventricular muscles are supplied only by the sympathetic fibers. Here there is a toxic nervous paralysis of the ventricular contraction in place of lack of force through degenerated muscle. When the intoxication is removed the contractile power of the myocardium improves the coronary circulation and the pain ceases.

This theory is offered after many years of clinical observation and many years of puzzled study. It does explain cardiac pain logically, and is borne out in each of its separate factors by experimental work in physiology and by known anatomy, and explains the baffling incongruous clinical symptoms and pathologic anatomy found in those hearts which have given pain through their functioning existence.

Summary. The most frequent cause of sudden death is not cerebral hemorrhage, but some cardiac lesion. Sudden death is not of common occurrence in heart disease when all forms of heart disease are considered.

Pathologic anatomy does not offer an explanation of cardiac pain.

Experimental evidence strongly indicates that the myocardial muscular tissue is insensitive, and does not cause pain by ischemia or failure of action through anoxemia or degeneration.

Cardiac pain is expressed only through the afferent nerves of the sympathetic portion of the autonomic nervous system.

Cardiac pain occurs when functional failure of normal reflexes produces conditions which stimulate the afferent nerve endings in the adventitia of the aorta and coronary vessels.

Experimental evidence also strongly indicates that vascular distention is the usual cause of cardiac pain rather than vascular spasm.

CONCERNING CERTAIN PHASES OF ANGINA PECTORIS BASED ON A STUDY OF 350 CASES.*

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I shall not attempt fully to discuss angina pectoris nor even attempt to consider all its most important aspects, for it is quite impossible for me to give an adequate discussion of this increasingly important syndrome in 1 hour. I have, therefore, chosen rather to present to you for thought and consideration only certain phases of the problem which have particularly intrigued me in my study of these cases in my hospital and consulting practice during the past 5 years. Much, if not most, of our opinions in regard to this fascinating condition are now undergoing very rapid evolution. I am also very far from believing that my present opinion in regard to any aspect of the problem is final or satisfactory. The subject is of more importance since the syndrome is undoubtedly rapidly increasing in occurrence and, directly or indirectly, it covers a very considerable part of the great problem of circulatory disease with which the medical profession is now so industriously concerned. Lambert says that in 1924, 22 per cent of the deaths in New York City were from cardiac disease, 2.5 per cent were of angina pectoris.

It is obvious that angina pectoris is not a disease entity but rather a symptom complex caused by at least several different pathologic states. Yet this picture is so definite in its appearance and so characteristic and dramatic a clinical entity, so very important a problem in every respect, that we should not, in my opinion, attempt to displace the term by anything more definitely allied to a more specific pathology.

The condition is always a serious one in which great disability and frequent death occurs. Ordinarily both its onset and its termination are of such a tragic type I am sure that most of us share with the intelligent laity a most wholesome fear of it. A constant menace of sudden death should always be conceded, and often this termination is of such an unheralded character that both physician and layman are always seriously impressed with the diagnosis. We

* Read before the Philadelphia County Medical Society, February 11, 1931.

are none the less more and more coming to realize that many cases, even severe instances of the syndrome may persist for years without causing either death or great disability. It seems to me also that our better understanding of the condition has led us to so treat it and to so manage our patients who are sufferers from it that they may in not infrequent instances occasionally live long, successful and useful lives even though subject to the condition. I feel that as we come to understand better not only the disease but also the individuals who suffer from it, we are able to offer a much more cheerful prospect to the sufferer. If we sufficiently individualize treatment we are much more likely to give relief as well as a prolonged and not inconsiderable period of worthwhile life and efficiency. Most of us can now cite unmistakable instances in which complete relief, even "cure" if you like, has been effected.

I think that all of us will admit that the condition is now much more frequent than was the case in the not remote past. Twenty or 30 years ago the disease was relatively rare in the so-called hospital classes. I have an explanation to offer for this fact, one other than that of better diagnosis of the complex. A few years back it was considered almost as a disease of the intelligent aristocracy, and as particularly of great frequency among our own and other professions, a disease of the "intelligentsia," if I may so say it. This distinction, in my observation, no longer pertains. I am finding angina frequent in my wards at Bellevue Hospital, which is one that caters I may say exclusively to the most unfortunate classes of our people. In my analysis of these cases at the hospital I have found almost without exception the disease associated with worry and great stress of life. These features are no longer confined to the so-called brain worker. Every class of society is now living lives of great and increasing emotional stress. The obligatory demand presented to every person, physical or brain worker, is for more speed, greater production and greater stress in every relation.

The statistical data which I have utilized in the preparation of this paper have been taken exclusively from my private consulting practice. Of the series of 350 cases studied 75 persons, including most of the women, were engaged in domestic occupations. But 19 were physical laborers, including policemen, soldiers, firemen and the like. Thirty cases were of the learned professions, 15 were engaged in artistic callings, 8 were financiers, 3 engineers. Fifty patients occupied executive positions and 93 were engaged in business ventures. This list suggests, of course, an increased occurrence among executives and business men. As in all lists of this kind, the decisive ratios are largely influenced by the preponderating character of the clientele which comes to any particular physician.

It is my impression that the complex is of growing occurrence among women, due, perhaps, to the increased stress of life to which

they are obligated by the modern vocations of women. Osler reports of 200 cases only 44 among women. My data also show a very high preponderance of men, notwithstanding the fact that my practice is about equally divided between men and women. Two hundred and seventy-two men are recorded in my data as compared to 88 women.

The cardinal symptoms of angina pectoris are familiar to all. It seems to me that the more simple that we keep them, the better able we shall be to visualize the problem, yet I shall venture to recapitulate them for the sake of clarity of discussion. Certainly the most outstanding symptom of the condition is pain. This was the dominant symptom in my series, being present in some degree in all cases. Pain is located almost always in the precordium and is oftentimes reflected in various directions, most commonly into the left shoulder and arm, but also upward into the neck, occasionally to the right arm and shoulder, or in other instances to wide distant areas, sometimes in the region of the appendix, to the rectum, the testis or ovary, the urethra, almost anywhere. Familiar as we are with the condition, during almost any week in my hospital cases are diagnosed as acute gall bladder disease, providentially in most instances the patient is considered as too gravely ill to justify immediate operation and the final diagnosis is usually made at autopsy; but the clinical diagnosis, based on history, for the patient enters in shock, perhaps had been cholecystitis with possible ruptured gall bladder. At autopsy these cases are found to have been usually instances of coronary thrombosis. Eleven such instances are recorded in my 350 private cases. The question of the reflection of pain, a striking symptomatic feature in about one-third of my cases, has been very adequately discussed in the literature many times. I refer particularly to the text of Mackenzie, of Alexander Lambert and many others. Vasomotor shock and various evidences of vascular spasm are other characteristic symptoms of the condition; they are present in nearly every case in more or less degree.

The most interesting symptom of the entire picture, and that which most impresses me as of primal importance, is the symptom of angina, as distinct from that of mere pain. It is the most striking symptom in about 40 per cent of my cases. The anxiety, the terror which is so characteristic and almost invariably present during the attack, quite independent of the knowledge of the patient, or even of his desire to live. In physicians, absolutely unafraid of death, entirely understanding of the nature of the symptom and perhaps perfectly accustomed to it, it is just as terrorizing as to an ignorant or absolutely nonunderstanding person. This phase of the complex seems to be more closely associated with an emotional state, with a disturbance of the psyche rather than with merely a local vascular disturbance.

The condition of vascular spasm, and especially its effect on blood pressure, seems to be considered by the profession at large as associated with general hypertension. But 96 of 350 cases showed hypertension and in at least one-half of these instances the hypertension was not a result but a remote cause of the condition. On the contrary, during the actual attack the blood pressure is most commonly lower than the customary blood pressure of the individual, nor is the symptom complex, in my experience, more frequent in instances of hypertension than in those who have low pressure figures. In 200 of my cases the pressure was held well within normal limits; in 54 the pressure was subnormal. As a rule, in the attack, as in all other forms of shock, the general blood pressure is depressed during the spasm. How it may be in the heart itself, or in the coronary vessels, I leave you to speculate. This is not to be considered as contraindicating the use of the vasodilators in the relief of the attack. I have never seen the nitrites to do otherwise than give benefit even in hypotensive cases, though, as you all know, they are often useless insofar as the stopping of the attack is concerned.

Admittedly the most difficult diagnostic point is the differentiation of true cases of angina from those conditions in which angina pectoris is closely simulated by phenomena which have in themselves no serious menace. Time-honored custom has grouped these conditions under the heading of pseudoangina. I see no real reason why this term should not be preserved. My distinction, and that which I find is commonly accepted by most active clinicians, is based on prognostic values almost entirely. It is recognized by all of us that the mildness of the attack is no proper measure or essential criterion, for in many of these instances the danger to life is quite as great as in those in which the suffering is prolonged and very severe. The distinction must then be based on the presence of anatomic lesions and, to a certain extent, on etiology.

In pseudoangina anatomic defects do not exist in the heart or aorta, whereas in true angina pectoris I hold that lesions exist to a recognizable degree in practically all instances. The time and the occasion do not permit me here to enter more than superficially into this differentiation, but practically all cases of pseudoangina may be grouped under the heading of psychic and emotional phenomena. They are tremendously frequent, particularly now that the laity has become so conversant with medical or pseudomedical literature and because of the agitation which we ourselves have started for the purpose of acquainting the public with medical matters. For each true case of angina which I see, I am certain that at least 3 instances of false angina present themselves in my office. As a rule, the differentiation is not difficult, for most of those who come with the spurious article are obviously neurotics. Many of them are so well educated in the symptomatology of the

disease that their history is most misleading and difficult to evaluate until the physician becomes sufficiently acquainted with the patient to judge the credibility of his story by the character and traits of the would-be patient. Quite naturally, physicians, medical students and nurses comprise a large proportion of the cases of pseudoangina. When the physician is permitted, however, to view his patient during one or two attacks, few mistakes in differentiation will occur. The picture of angina pectoris is certainly one of the most characteristic in medicine; combine such an observation with a diligent search for lesions and with a detailed historical and physical study of etiology, and the careful physician will make few mistakes. Unfortunately, however, neurotics may frequently present possible etiologic factors worthy of full credence, and even anatomic lesions also may be present which justify the more serious diagnosis. Of course, there is no reason whatever why the pseudo case may not ultimately develop a true complex, still when one can see the attack or secure a description of it from some credible witness, mistakes will not frequently occur, especially if the case can be held under observation for a reasonable length of time, and be seen during the attack.

Toxic angina is another clinical picture which, in my opinion, should be carefully separated from true angina, if we are to study the disease with any scientific satisfaction. In my experience there are just three toxemias which produce a picture easily confused with true angina pectoris. They are those produced by the abuse of tobacco, coffee and tea. The first, that produced by the abuse of tobacco, or in some instances developed as a result of an abnormal sensitization to tobacco, is exceedingly frequent.

In but 4 cases of true angina under my observation has tobacco been a possible causative factor; it is a common productive factor in toxic angina. This relation is becoming more and more important since women have so widely taken up the use of tobacco, for as a class women are far more susceptible to the bad effects of tobacco than men. They are also for various reasons much more likely to carry the use of the weed beyond, far beyond, the mere employment designed to give pleasure and a feeling of content to the formation of a definite injurious habit. I am prepared, however, to admit with very few qualifications that the use of tobacco is undesirable in true angina pectoris, that it tends to augment the severity of true attacks, to increase their frequency and to greatly increase the danger. I know, however, of no authoritative study which has shown that tobacco can produce any changes in the heart muscle, in the coronary arteries or in the aorta which are capable of causing a true angina. I have never seen a case of supposed tobacco angina die, except that there were found after death lesions quite typical of those which cause angina pectoris and which cannot be produced by tobacco alone. I have seen many instances of

tobacco angina which were very distressing. I have seen patients so sensitized to the effects of tobacco that they might not enter a room in which smoking was going on without developing an attack, a clinical picture which is almost the exact counterpart of a true anginal attack, but I have never seen such a case die. Almost without exception, prompt abandonment of the drug in persons who have developed tobacco angina is followed almost if not quite immediately by a cessation of the attacks. I have seen no treatment in true angina which is so successful.

Coffee angina is much more frequent in advertising literature than in medical reports. It is not often seen in the consulting room or the hospital, but it does exist. It, too, is promptly relieved by the elimination of the drug or by cessation of its abuse. Attacks rarely proceed beyond the point of a vague, infrequently reflected discomfort or mild pain in the region of the heart. Coffee is quite incapable of causing in the heart lesions similar to those essential to the production of true angina pectoris. Most of us now employ in the treatment of angina drugs similar to or identical with the essential principles of coffee, theobromin, theocalcin and caffein. My experience leads me to feel that in those instances in which angina appears from the abuse of, or unusual sensitization to coffee, the attacks are brought about by overstimulation of the nervous system and probably, therefore, the mechanism is quite similar to that manifested in pseudoangina pectoris. I am reasonably certain also that at least some of the cases are purely imaginary, perhaps stimulated by the advertising pages of our cheaper grade magazines.

I have never seen a case of angina caused by the abuse of tea. I believe, nonetheless, that they do occur, but probably in very small numbers, save in populations which consume tea in greater abundance than is customary in the localities in which I have practised. English and Canadian colleagues have described cases to me.

In all the toxic anginas almost immediate relief follows the elimination of the causative drug. Insofar as I can determine in none of the cases are any permanent lesions developed and the only treatment necessary is abstention from the drug. Sensitization to the drugs concerned in toxic angina may often persist for long periods of time, and the sensitization may become as acute as in any form of proteid sensitization so that infinitesimal quantities of the specific drug may suffice to precipitate the paroxysm. Insofar as I can learn, there are no cases of toxic angina on record in which electrocardiographic evidence of coronary spasm or embolism has been shown. Of course, any of these drugs used to excess may produce electrocardiographic changes, but not those typical of an angina pectoris of the coronary type.

Etiology and Pathology. In my opinion one of the most important phases of the subject of angina pectoris is the study of its pathology and etiology. The two are indissolubly blended. It has been this

phase of the question which has most interested me during the past few years and it is the study of this portion of our problem which should lead directly to a better understanding and command of the therapeutics of the disease.

Most authors mention in this connection that there are cases of angina, even fatal ones, in which absolutely no lesions of the circulatory system can be demonstrated. So many excellent authors mention this fact that perhaps we must accept it; but always the question remains of how carefully the tissues of the heart muscle and of the coronary vessels in particular were studied. I can recall but 1 of my angina autopsies in which I was unable to find what I considered adequate lesions in the heart or aorta. In this instance, however, no microscopic studies were made; therefore, knowledge of the numerous microscopic alterations in the muscle which might exist without gross recognition and which might nevertheless be quite sufficient to cause death. From a theoretical standpoint, there is no reason whatever why spasm in otherwise adequate coronaries might not cause death, and I have no doubt whatever but that such cases may exist. As a rule, instances of vascular spasm are not limited to a single field, for example, intermittent claudication is very common in angina of coronary origin, and the occurrence of vascular spasm elsewhere should always cause us to apprehend coronary spasm as a possible cause for angina pectoris. Ten of my cases showed claudication.

The intensive study of circulatory disease of the past 10 years has crystallized our conception of the basic lesions present in angina pectoris. Most of us now agree that the typical picture of angina pectoris may be produced by any one or more of four frequent lesions. In many instances they are associated.

Disease of the Coronary Arteries. This may cover a very wide field. No doubt the most common lesion of the coronary vessels is an endarteritis which produces nodal strictures of the lumen. This is probably associated with a certain degree of spasm during the attack. Ordinary arteriosclerosis of the coronaries is also a very frequent change. It may occur as a part of a general process of arteriosclerosis or it may exist in very severe degree in the trunks of the heart wall with but little general involvement outside this distribution. About 45 per cent of the cases of this study were clearly of this type. Aneurysmal dilatations are seen in some cases; in a few there is an active ulcerative endarteritis, probably with the formation of ultimate thrombosis in many instances. Calcification is common, especially in old age, and periarteritis may so constrict the lumen of the vessel as to bring about attacks of angina. Finally embolism, total or partial, brings about typical anginal attacks, with the subsequent typical clinical picture of coronary thrombosis and cardiac infarction. Eighty-five of the 350 cases of this series thrombosed. All of us believe that these lesions of the coronary

vessels or of any portion of the coronary system may cause typical angina pectoris. Studies of pathologic anatomy, however, in association with clinical observations show us beyond any possible question that any, or even all, of these lesions, even complete thrombosis of the coronary vessels may exist without producing anginal symptoms. It is evident then that this pathologic anatomy is not specific to the disease. There is doubtless some additional determining factor which decides in any instance those cases which on the basis of these lesions shall produce the clinical complex and those which will not.

There are many cases of angina pectoris in which insofar as we are able to determine there are no changes in the coronaries and in which the determining focus seems to reside in the aorta. There is a possible clinical distinction between these cases; it is not a hard and fast one, but it is helpful. In the cases of coronary origin the pain reflection is, as a rule, down the arm, whereas in those instances which develop as a result of aortic lesions the pain reflection is most commonly up into the neck or is located in the manubrium sterni.

Aortic Disease. The changes most commonly seen in instances which originate from aortic disease are located in the conus, and in many of these there is dilatation or sacculation of the sinuses of Valsalva. That there is an intimate association and confusion between aortic and coronary disease is indicated by one of the most frequent forms of aortic disease. This is the growth of the subendothelial fibrosa, so that the inner endothelial layer is erected upward into little mounds which appear with greatest frequency at the mouths of the coronary vessels and about the openings of the vasa vasorum. Under certain physical conditions it is readily understood why an obstruction of bloodflow into the coronary trunks is affected, so that the ultimate effect in this type of aortic disease is that of coronary occlusion or asphyxia.

Simple aortitis, cases in which the vaso vasorum are surrounded by an exudate of small round cells, cases of extensive ulceration with the laying down of fibrin clot, the strictures of cicatrization, cases in which large calcific areas and lesions are found—all these may also apparently cause angina pectoris. About 50 per cent of my cases showed aortitis of some degree or form. Again we must also confess that any or all of these gross anatomic alterations may be present without causing any symptom whatever of angina pectoris. Again it seems that we have not even here discovered a lesion specific to the syndrome, certainly not one specifically determinative of it alone, yet this is one of the most common pathologic anatomic pictures clearly causative of angina pectoris.

Myocardial disease is one of the most frequent causes of angina pectoris. This is a fact which is not adequately recognized by many clinicians. There may, perhaps, be some minor deviations from the

classical clinical picture of those cases of angina which develop from myocardial in contradistinction to those which appear in cases from coronary and aortic disease. Thus, for example, in these cases, as a rule, pain is not reflected characteristically into the arm and shoulder, but is more likely to be described as precordial in character, a dull aching pain usually of more constant duration than in either of the other forms and, as a rule, it is more usually developed as a result of physical stress. Unlike the other anatomic types, it is likely to be characterized by dyspnea and edema; otherwise this lesion gives practically the same picture as other forms.

The lesion in this type is very variable, depending on the origin of the defect and its chief point of location. It may appear in an acute condition, such as diphtheria, scarlet fever or other similar conditions which produce an acute parenchymatous degeneration of the myocardium. It is exceedingly common particularly after influenza, and it is not infrequent after pneumonia. It is seen also as a result of the inflammatory and degenerative process in syphilis, in rheumatic fever, acute or chronic, in which one expects to find Aschoff bodies in the heart muscle. It sometimes occurs late in the thyroid heart, in which a brown atrophy has developed. Any disease capable of setting up either a myocarditis or a myocardial degeneration may develop this type of angina pectoris. It is most commonly seen, naturally enough, in cases of fibroid heart from any cause whatever. The lesions may be, therefore, acute or chronic; some of the acute conditions are from their nature remediable, others, as in fibrosis, are invariably progressive. In those instances in which the most extensive lesion is distant from the main coronary paths, the electrocardiogram is quite different from the form most frequent in coronary cases and, of course, the electrocardiogram is that of a myocarditis and not that of coronary block.

There may be still other anatomic lesions which are capable of producing angina pectoris. It has been stated by some, for example, that certain pericardial lesions may cause the disease; this is, of course, conceivable if one assumes that the pericarditis extends into the myocardium and similarly a like process may be assumed to explain these cases which appear in association with endocarditis, either acute or chronic. Obviously in this, as in the other more frequent types of pathologic anatomy of angina pectoris, very profound myocardial lesions may exist without the least symptom or sign of angina.

When one classifies thus the pathologic anatomy of angina pectoris it is seen that its etiology must be exceedingly diversified. The extent to which this is the case has been, perhaps, insufficiently recognized by the profession.

In the *etiology* of angina pectoris I think that we must all recognize the tremendous importance of heredity. Nearly every practitioner of experience has families on his list who show a very definite

familial tendency toward the complex. It has been the most frequent manner of exitus in my own family for three generations at least. In many other instances a history of familial tendency toward cardiovascular disease is to be made out. As a rule, this is manifest in those families which develop early arteriosclerosis or who, having a natural tendency to long life from a perhaps natural degree of atherosclerosis, finally arrive at the stage of a generalized arteriosclerosis and angina pectoris. The anatomic lesions most prevalent in these familial cases is that of coronary disease, next aortic disease and last of all the myocardial lesions.

Arteriosclerosis is also independently a frequent factor causative in many instances in which no hereditary influence is to be found. In some instances, as in syphilis, lead and gout, there may be a definite cause for the arteriosclerosis evident, but in many other cases no cause may be thus apparent. It seems in very many cases that it is not the degree or type of the arterial disease but the individual peculiarity which determines whether or not the case will manifest angina. Hypertension is a factor in some cases beyond doubt; but no frequent relationship between hypertension and angina pectoris is seen in the series of cases which is the foundation of this study, though the cardiovascular-renal complex was a probable cause in several. Hypotension is, indeed, more frequent than hypertension, but it occurs as an incident and probably not as a causative factor, though Mackenzie evidently believed differently on this point.

Age alone does not seem to be a very great etiologic factor, though the syndrome is, indeed, rare except in adult life. One of Heberden's cases occurred in the second year. In this series statistics show the following:

One case only developed in a patient between 20 and 30 years of age; it was an instance following severe influenzal infection and was probably a result of myocardial disease. Ten cases appeared between 30 and 40 years, 72 between 40 and 50 years, 130 between 50 and 60 years (that period of greatest emotional stress), 101 cases between 60 and 70; 24 cases between 70 and 80 and 1 between 80 and 90 years. Age as the chief etiologic factor was noted in but 7 instances.

It has long been considered as an axiom that syphilis and angina pectoris are very frequently associated. Indeed, I too held that prevalent opinion, until actual analysis of my own cases convinced me that I had probably overestimated this factor (13 cases). Syphilis may produce all three types of lesions characteristically mentioned as productive of the complex; perhaps it is most commonly associated with aortic disease, but I have found it by no means thus proportionately causative of the syndrome. Paul White has apparently arrived at a similar conclusion.

Thrombosis or embolism is frequently found postmortem in

angina pectoris. In most instances, however, the thrombosis or embolism has apparently taken place in cases which have suffered from angina for some time previously. It is, therefore, more a result than a cause. There is also a not inconsiderable group of cases in which embolism or coronary thrombosis takes place in the course of angina and causes, instead of an increase of symptoms, an actual relief. I have already a group of some 15 cases under study in which this took place. Obviously all of these instances must have been of coronary origin, and this small group tends to emphasize the importance of coronary spasm in the induction of the clinical picture; for it is only conceivable that it is in such instances that relief of the symptoms can follow a thrombosis. It has at least been probably as effective in the cure of the syndrome as surgical measures, and while it in no way cures the disease, it stops its symptomatology very much as the various surgical procedures may do, at the probable expense of depriving the patient of the warning benefit of pain. In thrombosis there is a certain definite increased crippling of actual cardiac reserve, through the resulting myocardial defect resulting from the infarction and the adjacent myocarditis and degeneration.

Nothing can appear more obvious to the ordinary student of this subject than that the most frequently associated etiologic factor with angina pectoris is emotional stress. No other one immediate factor is so dominant in the precipitation of the immediate paroxysm and the very tendency of the disease chiefly to manifest itself in certain occupations and types of individuals is further illustrative of this fact. It is those concerned with the stressful phases of life that are chiefly affected by the syndrome, and it is during periods of emotional stresses that the initial paroxysm almost always appears. It is advanced by many that this fact in itself is a powerful argument, indicative of the arterial spasm theory of production, and this argument is further carried out by the frequency with which other spasmodic attacks of other vascular distributions appear in the same case. I wish in particular to mention the associated occurrence of intermittent claudication, abdominal anginas and the like. This association of other definite areas of arterial spasm in this disease has been observed in 81 of our series of cases.

Physical stresses as the cause of the symptom of angina is present in practically all well-established cases, the longer the standing, the more obvious does the relationship become. On the other hand, it is not those whose occupations entail great physical effort who chiefly develop the disease, but quite the contrary. Physical stress then should be considered not as a productive factor, though in established cases it is one of the most frequent immediately causative agents insofar as the individual paroxysm is concerned.

Diagnosis. It is not my purpose here to attempt to discuss diagnosis in any detail, for the reason that I think it far easier to make

the diagnosis in the individual case than to lay down hard and fast lines for diagnosis theoretically. My experience as a consultant has been that the average physician, surgeon, obstetrician or pediatrist is usually fully informed on this phase of the subject, and I do not believe that it requires any special consideration; but there are a few factors which my experience has led me to wish to emphasize on this question of diagnosis.

Obviously the chief problem is the distinction from pseudoangina which I have already in part discussed. In diagnosis, considerable attention and weight must be accorded to an estimation of the credibility of the patient on the degree and character of his pain. So many of the public are so well informed on these symptoms that they are likely perhaps unconsciously to tell a conclusive story of the disease through their very fear of it. An attractive and brilliant young woman, in her early twenties, recently came to my office with an almost letter-perfect recital of symptoms, and her suffering had become so severe that her brilliant future as a musician was seriously threatened. She almost persuaded me that she had true angina, so accurately did she describe it. Fortunately she permitted me to conduct experimental tests which I could never encourage in cases supposedly anginoid, for I exercised her to the extent of exhaustion without inducing an attack. The electrocardiogram was entirely negative. She was hypotensive, very suggestive, appallingly emotional; but absolutely no physical signs could be detected which could account for a basic pathology. I finally submitted her to very distressing emotional stress which induced an attack, and the nature of that attack at once persuaded me that we were dealing with an anxiety neurosis; for the patient was voluble with her symptoms *during the attack;* she could not remain at rest, but walked back and forth in the examining room; there was no cardiac arrhythmia—she was evidently in severe distress, but definitely not from an angina. A frank statement backed with a lack of all contributory pathologic anatomy finally succeeded in persuading the young woman that her attack was purely an emotional reaction and accompanied by no danger or real cardiac disease. She has had no subsequent attacks, and I confess that I have been much relieved also, for she nearly had me persuaded that she really had an angina.

The point is that observation of the attack is the most highly diagnostic fact. In my opinion the second most important fact is the determination of an adequate pathologic foundation. A failure to obtain some degree of amelioration under the nitrites is a strong negative point in difficult diagnosis. Always the elimination of emotional and hysterical states is a difficult matter. In some instances, of course, a knowledge of the personality of the patient is absolutely necessary in this respect and such an evaluation is always of great assistance in diagnosis.

There can be no question as to the high value of the electrocardiogram in the diagnosis of angina pectoris when it furnishes positive evidence. Negative electrocardiographic findings are of no value however either in a positive or a negative way. Frequent observers have reported entirely negative electrocardiographic findings even when taken in the height of the attack. Three such instances have fallen under my own observation, and in all the diagnosis was subsequently fully established—in 2 instances by death and in 1 by autopsy. Neither are electrocardiographic findings constant. In a recent case seen by me in consultation with Dr. Rabinowitz, of the Brooklyn Jewish Hospital, during a quiescent phase the electrocardiogram showed an absolutely positive picture, but during an attack 2 days later the record obtained by the same technician with the same instrument indicated absolutely no abnormality. This case was confirmed in diagnosis by an extensive coronary thrombosis a few days later.

Treatment. In many ways the most interesting subject in our present-day study of angina pectoris is that of treatment, and such is the importance of the subject that it warrants considerable discussion.

The question is frequently asked both by the physician and layman, Can angina pectoris be cured? In the past it has been largely the custom of many of us to answer such a question with the statement, "Only in cases of mistaken diagnosis." Our study of the pathology of the complex, however, in the past few years, associated with clinical observations which permit of little opportunity for error in diagnosis has led us to the answer that angina pectoris can be cured in instances in which the basic fault can be rectified. Obviously those cases founded on coronary and aortic lesions are the most difficult of cure in this regard, but many of the cases in which the basic fault is located in removable or curable lesions of the myocardium can certainly be cured.

I have seen cases caused by syphilis, believed to have been based on coronary or aortic lesions, which apparently underwent complete cure, though even in these most favorable instances there was in all probability some definite subsequent limitation of cardiac reserve nontheless. Many cases presenting quite characteristic clinical pictures, and a few with electrocardiographic positive evidence in which the basic fault lies in the myocardium, become apparently cured. I speak particularly of instances which arise after the acute infections, especially after influenza, pneumonia, tonsillitis and the like. Some cases apparently of rheumatic origin also have appeared to improve to the point of practical recovery, though almost if not always with some subsequent limitation of cardiac reserve. I am certain that we have permitted the lay public to become convinced of our undue pessimism in regard to this disease, and our pessimism has led in many cases to ineffective treatment on the

part of the doctor and inefficient coöperation on the part of the patient. My optimism, particularly in regard to syphilitic cases, I find has led me to be misquoted in some instances. Because early and efficient specific treatment will cure early cases of luetic angina pectoris in many instances, clinicians have concluded that any case due to syphilis should be cured. This is, of course, very far from the truth. When fibrosis has taken place, either in the heart muscle or in the walls of the coronary or aorta, it is not to be expected that cure, which is obviously dependent on removal of the underlying lesion, can take place, though it is perfectly true that in a very high percentage of these cases great benefit symptomatically and not infrequently a staying of progress can be effected, one can never tell except by therapeutic experiment.

Disappearance of symptoms is very frequent, and it occurs in very many instances, particularly if the treatment is properly administered and introduced before grave tissue changes have taken place. Disappearance of symptoms, however, is usually associated with a degree of permanent cardiac disability.

I have seen apparent complete relief follow in 2 cases probably caused by gout. Both signs and symptoms entirely disappeared under proper diet and medication. A few cases of what I took to be true angina pectoris have received symptomatic cure from the relief of secondary subsidiary factors. Thus I have seen symptoms subside from the giving up of tobacco, the cessation of violent exercise or from a better control of the temper. It is most important in the treatment of individual cases to take all these factors into full consideration.

Discussion of treatment resolves itself naturally into the treatment of the underlying disease and that of the paroxysm. The former is, of course, the more important; but primary effort is to give relief to the acute attacks and insofar as possible to prevent the onset of others. I am convinced that there is such a thing as an anginal habit, *i. e.*, that one attack predisposes to another, and if attacks are never allowed to eventuate or to come to a climax there is a definite tendency toward less frequent attacks, the habit tendency instead of increasing, as is usually the case, becomes lessened. For this reason I think it important that the patient should promptly use his nitrite or such other measures as may be efficient in preventing the development of the complete attack. Rest, elimination of tobacco, attention to abdominal distention, a diet suited to the particular case under study, thorough emptying of the bowel and especially control of the emotions should be practised insofar as possible. In this regard, there is a well-known fact infrequently mentioned in the literature, but exceedingly important and well recognized by most clinicians, namely, that sexual excitement is exceedingly inadvisable in these cases. The number of cases which die under such conditions is large.

It is hardly necessary to enter closely into the discussion of treatment of the acute paroxysm. The best methods are well recognized; there are few but most insistent demands and the drugs which we have at our disposal are not numerous. The one drug which will give the most relief in severe attacks is morphin. I have seen instances so severe that as a humanitarian measure, I gave chloroform. I have never had a patient die under the drug, and I believe that it is justifiable in some instances. Morphin will usually suffice, but it must be given courageously. Very recently I saw such a case which had been under chloroform for several hours; recovery followed.

Many attacks are immediately relieved by the nitrites, either the inhalation of amyl nitrite or by the taking of nitroglycerin by mouth or by hypodermic. There is nothing in the theory that nitroglycerin acts more quickly when given by holding it under the tongue than when it is swallowed. The liquid preparations of nitroglycerin are usually more efficient, and it is wise for the patient to carry in his pocket a small phial of spirits of glonoin freshly prepared each day for emergency use, unless perchance it has been found that the tablets, usually hypodermic ones, are equally efficient. When the ampules of amyl nitrite are found effective they are perhaps most convenient, but they are usually not so prompt in effect as nitroglycerin. Even in the management of these acute attacks you will find that a singular amount of individual peculiarity exists, and it is well worth while to try to study out these special reactions so that your patient may always receive the maximum benefit as promptly as possible. Of course, when coronary embolism occurs a special line of treatment, which involves the liberal use of morphin, chloral and profound rest, must be instituted.

When the paroxysms are very frequent and severe, confinement to bed is advisable, at least until it can be experimentally determined that the attacks are not decreased by this measure. There are unquestionably many cases which do better if allowed up about, and some at their customary occupations. In this respect, as in all others in this problem, it cannot be too insistently emphasized that individualization is absolutely essential in the treatment of this condition; it is imperative. Exercise is another matter which must be determined only by experiment. Usually it should be diminished merely to that of necessity, but there are exceptions. So great is the emotional factor in this complex that it is often better to permit the patient to do at least some of his ordinary work, if thereby he is rendered more content and happy. I have had many instances in my experience which demonstrate this point. Throughout it must be most positively recognized that in this disease emotional stresses are even more important than physical ones.

These general measures having been instituted, the next most important thing is to attack the underlying cause. In case it is

due to syphilis, specific treatment must be given, and it is inadvisable to use the arsenical preparations until the patient has first been brought well under the effects of mercury, iodid or bismuth. In case of a basic gout, colchicum, atophan and the alkalies, water and a suitable diet are to be enforced. In case the basic lesion is a myocardial degeneration, rest and the elimination of the causative factors insofar as possible are imperative requirements. The same is true of acute myocarditis, such as, for example, may occur in rheumatic fever. There can be but little doubt but that the salicylates in these instances sometimes at least effect much benefit. I have seen cases get more actual relief from the salicylates than from the opium preparations in these cases.

In fibroid myocarditis and occasionally also in myocardial degeneration digitalis occasionally gives great relief, both in relieving the severity of the paroxysms and in lessening their number. In coronary cases it gives little or no relief, and oftentimes makes the attacks more severe and frequent. It may be tested out experimentally, however. In all cases, except in thrombosis, the vasodilators are tremendously beneficial, and the nitrites, nitroglycerin, sodium nitrite, erythroltetranitrite and the like are all used successfully in the prevention as well as in the relief of attacks.

Sleep and rest are of crucial importance, and when they may not be obtained otherwise the opium preparations are advisedly, if not compelledly given. The vasodilator sedatives, led in efficiency by chloral hydrate and similar drugs, are preferably given at bedtime. Alcohol, recommended many years ago by Heberden and others of his time, has a very definite benefit in very many cases, especially among the aged and arteriosclerotic. It is a splendid preventive also. Such sedatives as the bromids, barbital and the like, may be employed habitually for long periods.

The spiritual side of the case must not be neglected in this disease in which the emotions play so important a rôle. The development of a philosophy of life, of the power of adaptation of desire to possibilities, the cultivation of hobbies of a restful character, such as suitable reading, music and such pacific occupations as painting, etching, carving and similar pursuits, are of real medical benefit. Habits of restfulness and relaxation are to be cultivated. Climate is often very important, and those who live in the temperate zones may well spend their winters in the South or perhaps go to live permanently in some mild, temperate and congenial climate. Few patients do well in the cold places or at high altitudes.

Meantime attempts at the maintenance of cardiac reserve must be made; the use of massage when exercise is impossible; a diet must be devised suitable to the particular needs and metabolic peculiarities of the patient.

If possible the patient should be seen at frequent intervals, at least until a complete and correct appraisal of the person as well as

of the disease and lesion has been made, and treatment should be adjusted to such needs, physical, mental and medical as the individual's instance will dictate. Some cases must not be kept too long in bed, but periodic times of rest in bed are very helpful.

The treatment of angina is not a hopeless attempt. If intelligently directed it will in very many cases prolong life and add tremendously to comfort and economic efficiency. A few cases you may cure.

EXPERIMENTAL CHRONIC HYPERPARATHYROIDISM.*

I. METABOLISM STUDIES IN MAN.

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AND

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SINCE the report in 1926 of Mandl's[1] case of osteitis fibrosa, in which the operative removal of a parathyroid tumor was clinically beneficial, a number of cases of bone disease have been reported for which overfunction of the parathyroid glands has been thought to be the underlying cause. These cases represent, for the most part, the generalized skeletal abnormality first clearly described by von Recklinghausen[2] and designated by him as osteitis fibrosa osteoplastica, but hypertrophy and tumor formation of the parathyroids have been noted also in osteomalacia and rickets, as well as in multiple myeloma and metastatic carcinoma. It thus was not quite clear whether hyperfunction of the parathyroids produced one sharply distinguishable disease or could be responsible for a variety of bone lesions and it seemed that the subject might be clarified by reproducing a chronic state of hyperparathyroidism in otherwise normal animals, and observing histologically and otherwise, the type of skeletal deformity which would result.

Our interest in the problem was aroused by personal experience with 2 cases of bone disease, in both of which parathyroid tumors were found. Further stimulus was given to our interest by the extensive metabolism studies of Aub and his associates[3, 4, 5] in which they injected parathormone into normal and pathologic human subjects and observed biochemical changes quite similar to those characteristic of patients with parathyroid tumors and by

* Read before the Association of American Physicians, Atlantic City, May 6, 1931.

their animal experiments[6] in which they demonstrated by gross examination a loss of bone trabeculæ as a result of chronic injections of parathormone.

Our aim was to provide a complete study of gross, roentgenologic and histologic changes in the bones of animals, subjected to chronic injections of parathormone, to determine whether the lesions were characteristic of one or more of the bone diseases mentioned and to observe whether the simultaneous administration of irradiated ergosterol would influence the results. Our interest in the effect

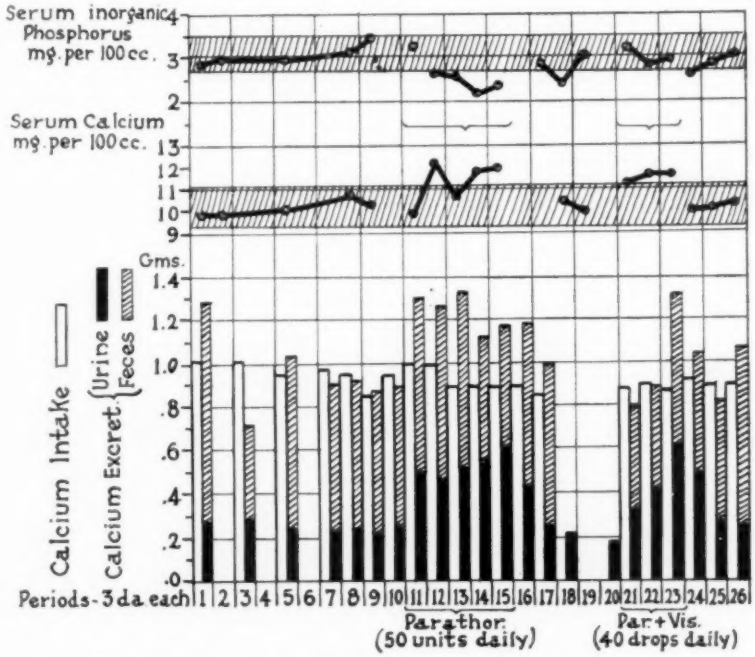

FIG. 1.—Parathormone experiment, October 14 to December 31, 1930, J. L. J., ♂, 35 years; height, 64¼ inches; weight, 131 pounds.

of the ergosterol was aroused by incompletely controlled observations in a case of fibroid osteitis[7] which had led us to infer that the course of this disease had been favorably influenced by vitamin D, also by the fact reported by Nonidez and Goodale,[8] Higgins and Sheard,[9] that deprivation of vitamin D led to parathyroid hyperplasia. There was a hint in this that fibroid osteitis was closely related to rickets and osteomalacia.

The study was made the subject of a thesis for the doctorate of philosophy by J. L. Johnson and the details of these experiments will be reported elsewhere by him. He began them in July, 1929, and had obtained very convincing results before we learned of the

similar studies of Jaffé and Bodansky. Johnson's[10] observations completely confirm those of Jaffé and Bodansky.[11, 12] The lesion produced by chronic injections of Collip's parathormone prepared by the Eli Lilly Company is a lacunar resorption of bone which involves both the trabeculæ and the corticalis, and is accompanied by the replacement of both marrow and bone by fibrous connective tissue, the process including cyst formation and the appearance of giant cells, and resulting in a histologic picture that so closely resembles the generalized osteitis described by von Recklinghausen[2]

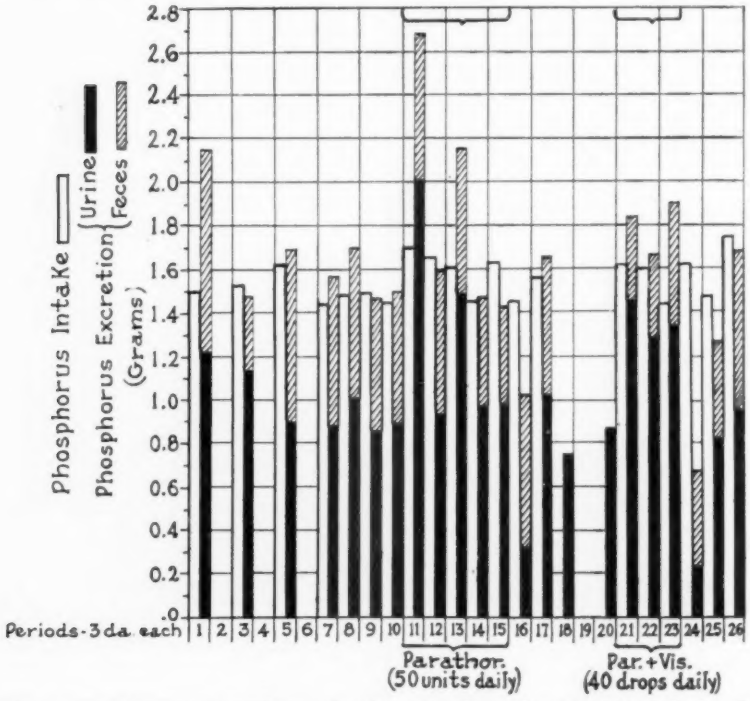

FIG. 2.—Parathormone experiment, October 14 to December 31, 1930, J. L. J., ♂, 35 years; height, 64¾ inches; weight, 131 pounds.

as to be practically identical with it. No lesion has resulted, in over 100 experiments in puppies, young dogs and rats, which bore so close a resemblance to osteomalacia, to rickets, or to any other bone disease. The experiments further reveal that the effects of parathormone injections are not counteracted by the simultaneous administration of irradiated ergosterol.

The dosage of parathormone in the case of the rats was usually 20 units a day and when viosterol was added, its dose was usually 15 drops a day. In the case of the puppies the parathormone dosage was increased progressively from 2 to 20 units a day. The viosterol given to puppies was 5 to 20 drops daily. It will be recalled that the

rat has been considered to be unusually resistant to parathormone. Our experiments show that this resistance is only relative and that proper doses of the hormone are definitely active.[10]

Two calcium and phosphorus balance experiments were included as a part of this study. These were made on two human subjects with a view to observing the biochemical and symptomatic effects of daily injections of parathormone, and in order to discover whether these would be influenced by treatment with irradiated ergosterol. The results in one of these experiments we wish to report at the present time.

The subject was a healthy, male, colored student, aged 35 years, 64.5 inches in height and 131 pounds in weight. He was engaged

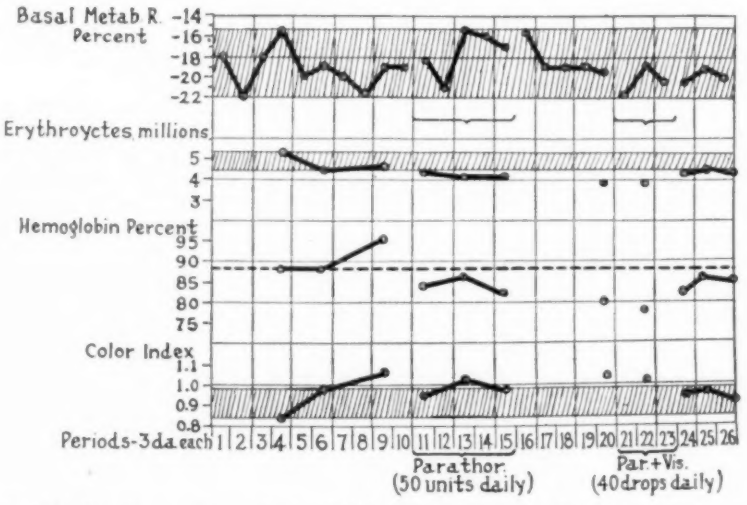

FIG. 3.—Parathormone experiment, October 14 to December 31, 1930, J. L. J., ♂, 35 years; height, 64½ inches; weight, 131 pounds.

in laboratory duties during the entire time. The technique followed in general that developed at the Massachusetts General Hospital,[13] differing, however, in that Bauer and Aub's diets had been rigidly limited in calcium (to about 0.1 gm.) in order to minimize the significance of unmetabolized calcium, whereas our diet was planned to contain just sufficient calcium, about 0.4 gm., to maintain a calcium equilibrium. The urine throughout the experiment was neutral to litmus, indicating a reasonable balance of acid base values in the diet. A slightly positive nitrogen balance existed throughout the experiment.

The diet was held rigidly constant for 78 days and actual control of it was maintained by direct analysis of 10 per cent aliquot portions (Table 1). These analyses were made in 20 of the 26 three-day periods. The fluid intake was held constant at 2000 cc. and the sodium chlorid at 3 gm. All water used for drinking, for the prepa-

ration of food, and for washing containers for food or excreta was distilled.*

TABLE 1.—COMPOSITION OF THE DIET.

Parathormone Experiment, October 14 to December 31, 1930.

Subject: J. L. J., aged 35 years; height, 164 cm.; weight, 62.2 kg.; diet, October 21 to December 31.

Food.	Grams.	Food.	Grams.
Orange juice	100	Butter	55
Apple sauce	200	Salad oil	10
Lemon juice	60	Egg white	120
Sugar	135	Steak	40
Ginger ale	200	Cheese	15
Lettuce	60	Cream, 40 per cent	100
Celery	30	C. P. Salt	3
Bread	120	Total fluids	2000

		Calories.	Nitrogen, gm.	Calcium, gm.	Phosphorus, gm.
By calculation		2215*	6.73	0.396	0.478
By analysis of 10 per cent aliquots†	Max.	..	7.69	0.336	0.572
	Min.	..	6.69	0.286	0.482
	Mean	..	7.04	0.307	0.522

* Basal metabolic rate 1230

† Aliquots of the food were prepared daily. These were combined in 3-day periods and analyzed. The diet of the entire experiment was controlled by such direct analysis.

The experiment consisted of a control or fore period of 31 days, a period of parathormone administration, in a daily dosage of 50 units, which lasted 15 days, a recovery period of 15 days, a period of 9 days with parathormone in the previous dosage plus 1 cc. of viosterol and a final recovery period of 9 days. Urine and feces were collected for analysis in 3-day lots, carmin alum markers serving for separation of the feces. The analytical methods are tabulated.[13, 16, 17, 18, 19] (Table 2.)

TABLE 2.—ANALYTICAL METHODS FOR METABOLISM STUDIES.

	Phosphorus.	Calcium.	Nitrogen.	Creatinin.
Urine	Fiske and Subbarow	Aub's modification of McCrudden	Kjeldahl	Folin
Feces	Fiske and Subbarow	McCrudden	Kjeldahl	
Food	Fiske and Subbarow to filtrate of ash	McCrudden	Kjeldahl	
Blood serum	Fiske and Subbarow	Clark and Collip modification of Kramer-Tisdall		

The biochemical results are shown in the accompanying charts and Table 3. The response to parathormone, like that previously reported by Collip,[14] Greenwald and Gross[15] and others, consisted of an elevation of the calcium and depression of the phosphorus of the serum, and a prompt, very markedly increased urinary

* The details of the preparation and serving of the diets used in this and other experiments to be reported from this laboratory, the preparation of aliquot portions of the diet, as well as the methods of collection and drying of excreta, will be the subjects of separate papers by Florence Smith, Lillian Eichelberger and their associates.

excretion of phosphorus and calcium. The data tend to support the view of Aub and his associates,[4] and of Albright and Ellsworth,[5] that the phosphorus metabolism is affected noticeably earlier than the calcium. The administration of viosterol with parathormone gave similar results except for a slight delay in the development of the maximal urinary excretions, both of phosphorus and of calcium. There was also some indication that a greater amount of both calcium and phosphorus were absorbed from the bowel. However, the effect of viosterol in this dosage was certainly not such as to demonstrate an antagonism in its action to that of the parathormone.

Daily determinations of the creatinin excretion, the nitrogen balance and the basal metabolic rate failed to indicate any metabolic alterations apart from those of the mineral metabolism. (Table 3.) A moderate anemia was observed, comparable to that reported in patients with parathyroid tumors. A very slight diuresis of short duration was observed as a result of parathormone administration.

The symptomatic response to medication with parathormone of this dosage (50 units daily) was of unusual interest. Muscular weakness appeared on the 12th day of the parathormone period. It was associated with a dull aching in, and tenderness of, muscles and bones of the arms and legs. Sharp, shooting pains followed, and a dull headache was complained of. These symptoms almost disappeared in the first recovery period but became worse than ever in the subsequent parathormone viosterol period, accompanied then by a sense of depression and loss of ability for mental work. Bone tenderness and muscle weakness were observed by Johnson[10] in his experimental animals. They are characteristic symptoms of fibroid osteitis.

Osteitis fibrosa osteoplastica has thus been reproduced experimentally in animals, in almost every particular, by the injection of parathormone. This convinces us of the correctness of the conclusion that the pathogenesis of this disease, as it is observed spontaneously in man, is an oversupply of parathyroid hormone. Lesions other than those characteristic of fibrous osteitis did not occur in over 100 chronic experiments with animals, from which we infer that the hypertrophies and hyperplasias of the parathyroid glands, noted in skeletal diseases other than fibroid osteitis, are secondary phenomena. The fact that viosterol neither significantly alters the disturbed calcium and phosphorus metabolism of hyperparathyroidism, nor modifies the histological abnormality of the bones of animals receiving chronic injections of parathormone, is evidence that osteitis and osteomalacia (rickets) are of different origin.

Summary. The repeated injection of parathormone has produced, in puppies and young rats, a uniform skeletal abnormality that is characteristic of osteitis fibrosa osteoplastica (von Recklinghausen). A lacunar resorption of the trabeculæ and corticalis of bones resulted, with replacement of marrow and cortex by fibrous connective tissue and osteoid tissue. Giant cells appeared and

TABLE 3.—METABOLIC DATA IN PARATHORMONE EXPERIMENT, OCT. 14 TO DEC. 31, 1930.
Subject: J. L. J. (Male), 35 yrs. Height, 164 cm. Average weight 59 kg.

Period (3 days each).	Calcium.					Phosphorus.					Nitrogen.					Urine.		Serum.				
	Intake, total gm.	Output.			Balance, gm.	Intake, total gm.	Output.			Balance, gm.	Intake, total gm.	Output.			Balance, gm.	Vol., cc.	Creatinin, gm.	Calcium.		Phosphorus.		B.M.R., per cent.
		Urine, gm.	Feces, gm.	Total, gm.			Urine, gm.	Feces, gm.	Total, gm.			Urine, gm.	Feces, gm.	Total, gm.				Max., mg.	Min., mg.	Max., mg.	Min., mg.	
I	1.018	0.274	1.021	1.295	−0.278	1.503	1.227	0.936	2.163	−0.660	20.1	22.2	2.6	24.8	−4.7	8105	4.06	10.4	9.3	2.9	2.8	−18
II	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	†9.9	9.9	†2.9	2.9	−22
III	1.017	0.296	0.428	0.724	+0.293	1.530	1.142	0.338	1.480	+0.050	20.2	17.4	1.4	18.8	+1.4	6625	3.83	....	....	....	....	−18
IV	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	−16
V	0.950	0.248	0.891	1.139	−0.189	1.637	0.901	0.792	1.693	−0.056	20.4	17.0	2.8	19.8	+0.7	6310	4.16	10.4	10.0	3.1	2.7	−20
VII	0.978	0.233	0.792	1.025	−0.047	1.446	0.880	0.697	1.577	−0.131	20.6	17.5	2.1	19.5	+1.0	5920	4.15	....	....	....	....	−19
VIII	0.966	0.249	0.792	1.041	−0.075	1.484	1.016	0.697	1.713	−0.229	20.1	17.4	2.1	19.5	+0.6	6260	4.01	*11.1	10.4	3.4	2.7	−20
IX	0.866	0.231	0.653	0.884	−0.018	1.494	0.866	0.598	1.464	+0.030	20.1	16.6	2.1	18.7	+1.3	5610	4.11	10.5	10.2	3.5	3.4	−21
X	0.947	0.252	0.653	0.905	+0.042	1.454	0.899	0.598	1.497	−0.043	20.6	16.8	2.1	18.9	+1.7	6165	3.99	....	....	....	....	−19
Parathormone started; 25 units twice daily.																						
XI	1.009	0.500	0.800	1.300	−0.291	1.717	2.012	0.674	2.686	−0.969	21.6	16.6	2.0	18.6	+3.0	6580	4.05	12.1	‡10.0	3.5	3.1	−20
XII	0.989	0.464	0.800	1.264	−0.275	1.658	0.940	0.674	1.614	+0.044	20.2	16.1	2.0	18.0	+2.1	5040	3.97	12.4	11.5	2.7	2.4	−21
XIII	0.893	0.519	0.800	1.319	−0.426	1.618	1.489	0.674	2.163	−0.545	21.0	17.2	2.0	19.2	+1.9	7180	4.01	11.0	10.7	2.6	2.2	−16
XIV	0.898	0.566	0.565	1.131	−0.233	1.456	1.028	0.448	1.476	−0.020	21.0	16.7	1.4	18.1	+2.9	6300	3.72	11.8	10.9	2.6	2.1	−16
XV	0.885	0.610	0.565	1.175	−0.290	1.639	0.987	0.448	1.435	+0.204	21.1	16.9	1.4	18.2	+2.9	5930	3.82	11.8	11.0	2.8	2.3	−17
Discontinued parathormone.																						
XVI	0.893	0.436	0.748	1.184	−0.291	1.464	0.393	0.639	1.032	+0.432	20.7	16.0	2.0	17.9	+2.8	5320	4.95	....	....	....	....	−17
XVII	0.857	0.264	0.748	1.012	−0.155	1.571	1.023	0.639	1.662	−0.091	20.9	17.0	2.0	19.0	+1.9	6145	3.92	....	....	†2.9	2.9	−19
XVIII	....	0.235	....	....	....	....	0.755	....	....	....	....	15.6	....	....	....	6190	3.68	†10.5	10.5	†2.4	2.4	−19
Viosterol started; 40 drops daily.																						
XIX	....	....	....	....	....	....	0.874	....	....	....	....	16.7	....	....	....	6465	4.20	†10.0	10.0	†3.0	3.0	−19
XX	....	0.188	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	−19
Viosterol continued, parathormone resumed, 25 units twice daily.																						
XXI	0.890	0.337	0.472	0.809	+0.081	1.631	1.465	0.382	1.847	−0.216	21.9	16.4	1.3	17.6	+4.3	6650	4.06	11.3	§10.6	3.2	2.6	−22
XXII	0.915	0.424	0.472	0.896	+0.019	1.615	1.291	0.382	1.673	−0.058	21.5	16.8	1.3	18.1	+3.5	6045	3.88	11.7	11.6	2.8	2.7	−19
XXIII	0.878	0.627	0.699	1.326	−0.448	1.447	1.357	0.558	1.915	−0.468	22.2	16.9	2.1	19.1	+3.2	6005	4.03	11.7	11.3	†2.9	2.9	−20
Discontinued para thormone and viosterol.																						
XXIV	0.933	0.492	0.544	1.036	−0.103	1.634	0.242	0.440	0.682	+0.952	23.1	16.2	1.4	17.7	+5.4	5415	3.84	11.7	10.2	†2.6	2.6	−21
XXV	0.905	0.285	0.544	0.829	+0.076	1.483	0.836	0.440	1.276	+0.207	21.9	17.4	1.4	18.8	+3.1	6520	3.93	†10.1	10.1	†2.8	2.8	−19
XXVI	0.911	0.274	0.812	1.086	−0.175	1.762	0.960	0.727	1.687	+0.075	21.6	16.5	2.0	18.5	+3.1	6210	3.91	†10.3	10.3	†3.0	3.0	−20

* Blood drawn 2 hours after breakfast.
† Only 1 determination during period.
‡ Blood drawn 6 hours after initial injection.
§ Blood drawn before first parathormone injection.

cysts were formed. The administration of viosterol together with parathormone did not modify significantly the end results.

The data of these animal experiments are reported in papers to follow. The present communication is concerned with observations of the metabolism of a normal human subject who was treated experimentally, first with parathormone, then with parathormone and viosterol. The characteristic disturbances of calcium and phosphorus metabolism produced by injections of parathormone, as well as certain symptoms, notably bone pain and muscle weakness, characteristic of osteitis fibrosa osteoplastica, were not significantly modified by the simultaneous administration of viosterol.

The results of these animal and human experiments confirm the view that the pathogenesis of osteitis fibrosa osteoplastica, as this disease is observed spontaneously in man, is an oversupply of parathyroid hormone and that this disease bears no relation, etiologically, either to osteomalacia or rickets.

NOTE.—It is a pleasure to acknowledge our indebtedness to the staff of the section of metabolism for their assistance and to thank Dr. G. H. A. Clowes and the Eli Lilly Company for generous supplies of parathormone.

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DIABETIC PYORRHEA.*

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DENTAL diagnosis may be divided into two general classifications: The effect of dental disease upon the various organs of the body and the effect of diseases of other organs upon the oral tissues. Dental focalized infection, though often empirical, has by its

* Read at a meeting of the Philadelphia Academy of Stomatology, April 28, 1931.

therapeutic results attained a recognized place in medical practice, while oral manifestations of systemic diseases are more often used by physicians than by dentists. Physicians value the strawberry tongue of scarlet fever, the bloodless mouth of pernicious anemia, the swollen, ulcerated gums of scurvy, the definite lead line of plumbism, the characteristic tongue of myxedema and pellagra, the extravasations of blood into mucous membranes in purpura and the yellow mouth of jaundice. The purpose of this paper is to touch both of these general classifications as observed in 138 cases of diabetes mellitus, and to dwell particularly upon the prevalence of pyorrhea in this disease.

The chief characteristic of diabetes is a disordered carbohydrate metabolism in which sugar is no longer properly stored in the liver and the muscles as glycogen, but circulates in abnormal quantities in the blood and finds its way through the kidneys into the urine. It is attended by dry skin, excessive thirst, marked emaciation and loss of strength. It exists in varying degrees of severity in different individuals and seems to be influenced by race, size and other factors. Unfortunate cases terminate either in gangrene of the extremities or the end comes through total failure of the body chemistry, with the tragic though merciful intervention of coma. All of these characteristics are perfectly familiar to the physician, but they are far less so to the dentist, and it is from the standpoint of the dentist that we must endeavor to approach the subject.

Prinz[1] has well suggested that theories as to the cause of pyorrhea should be classed as (1) salivary calculus, (2) infection, (3) occlusal stress, (4) constitutional disturbances and (5) alveolar atrophy. Diabetic pyorrhea seems to be the result of a constitutional disturbance.

Members of both the medical and the dental profession agree on the importance of eliminating oral sepsis from the mouths of diabetic patients, while some even claim that, as the oral infection subsides, the sugar is correspondingly reduced.

Another important factor in practice on patients with diabetes is the choice of time for all operative procedures. Unless the urine is free from sugar, and the blood sugar is kept within normal limits, wounds in the diabetic may fail to heal.[2] The use of insulin and the regulation of diet by a physician in coöperation with a dentist make it possible nowadays for these patients to have the benefits of dental surgery at any time it may be needed.

Another aspect of oral involvement in diabetes was reported by the writer in 1928.[3] Patients who have well-developed diabetes but have had no diabetic treatment exhibited the following characteristics: The teeth were loose; the gums were hypertrophied, inflamed and dark red, ulcerated and sometimes covered in spots with grayish areas of necrotic tissue. (Figs. 1 and 2.) This condition resembles pyorrhea, but it is not ordinary pyorrhea. It resembles Vincent's infection, but it is not Vincent's infection.

FIG. 1.—Type (1) diabetic pyorrhea. Note changes in gingival tissue.

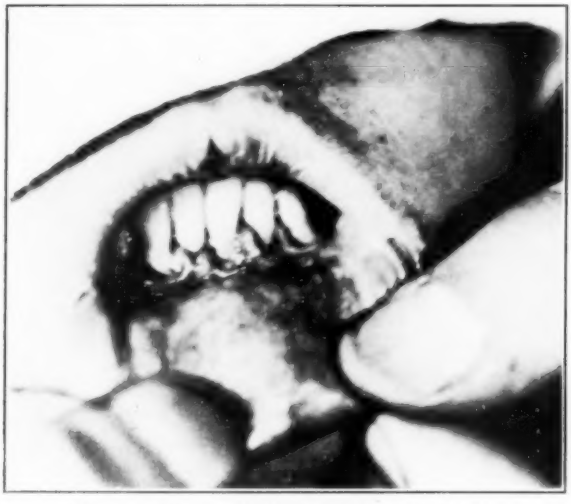

FIG. 2.—Type (1) diabetic pyorrhea in a child.

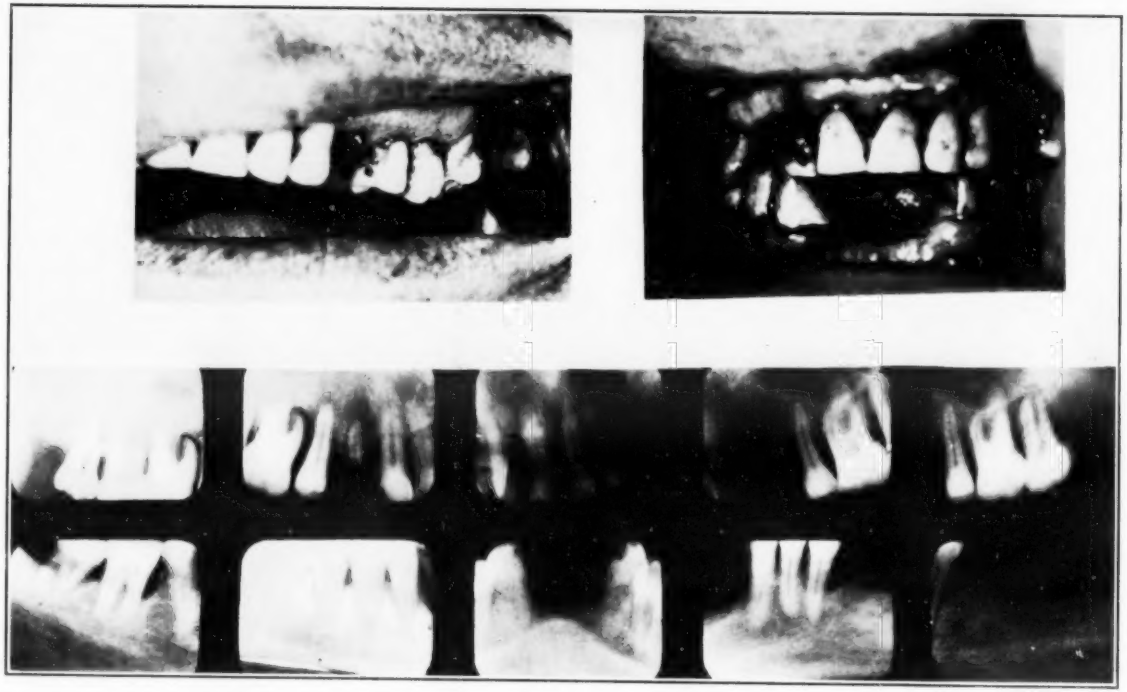

FIG. 3.—Type (2) diabetic pyorrhea. Note extensive loss of alveolar bone

It resembles mercurial poisoning, but is not mercurial poisoning. It resembles cancer, but is not cancer. It is believed to be a clinical entity.

Patients who had had diabetes for some time and who had been kept under diabetic control presented other changes. Their teeth were firm; the mucous membrane, while soft, flabby and spongy, presented no areas of ulceration, and the gums, as a rule, had not receded, but there was extensive loss of alveolar bone, together with deep pockets with but little or no pus formation. (Fig. 3.)

About half of the patients reported at that time were edentulous. They invariably gave a history of loose teeth, tightening at times before they became so extremely loose as to necessitate removal. Without exception, they related that the looseness of the teeth was noticed prior to or at the time of the discovery of diabetes.

Two Europeans have recorded this condition, one in 1899[4] and the other in 1907.[5] Inglis,[6] in 1908, noted that a predisposition to pyorrhea alveolaris was probable in patients suffering with diabetes. The statement that the teeth became loose in diabetes appeared in the *Encyclopedia Britannica*[7] for the first time in 1877. In an excellent classification of oral manifestations of systemic disease Bloch[8] included diabetic pyorrhea. Ersner,[9] in 1925, recorded the prevalence of pyorrhea in diabetes, and stated that, while he had not collected any statistics on pyorrhea associated with other diseases, he believed it more prevalent in diabetes. Rhein[10] introduced this subject to the profession in 1888. In 1894[11] he presented a classification of "pyorrhea" as follows: (1) Pyorrhea simplex, embracing all cases of purely local origin and requiring only local treatment. (2) Pyorrhea complex, embracing that larger field of more serious disorders and graver affections. Under "pyorrhea complex" he suggested the use of the terms "tubercular pyorrhea," "anemic pyorrhea" and "diabetic pyorrhea."

Winnett,[12] in describing diabetes from the standpoint of medicine, reminds us that glucose flows about in the blood stream and bathes every tissue in the body, making an excellent culture medium for bacteria. Whether his statement, that the reason the bacteria thrive is that glucose is actually a culture medium, is true or not will have to be left for final determination to students of internal medicine. According to this author, the bacteria of the mouth plus the glucose solution plus small abrasions cause these patients to have pyorrhea. Their poor resistance is explained by the fact that "their tissues have no comeback." In the light of biochemistry the question immediately arises as to the possibility of the absorption of bone being due to the continual acidosis of the patient.

This present study is limited to clinical findings, which have been more or less uniform in 138 patients. (Table 1.) Fifty-four of these patients were toothless, with a history of pyorrhea, 3 did not show any evidence of pyorrhea, while the rest (81) had definite periodontal disease.

TABLE 1.—ANALYSIS OF CASES.

Total number of diabetic patients	138
Number of children	3
Number of adults not showing pyorrhea	1
Number of children not showing pyorrhea	2
Total number showing pyorrhea	81
Number toothless	54
Number showing pyorrhea, or giving history of pyorrhea	135

The striking similarity of ordinary pyorrhea to diabetic pyorrhea would seem to indicate a reasonable possibility that some patients are being treated for pyorrhea when they should, at the same time, be treated by a physician for diabetes. The changes in the color, consistency, shape and character of the gums, together with the dry skin, thirst and loss of weight, certainly afford the dentist a suspicion useful for diagnosis.

Conclusions. 1. A study of 138 diabetics demonstrated that the oral cavities present certain characteristics in this condition.

2. These modifications of the dental tissues are so nearly constant as to constitute a clinical entity.

3. The number of pyorrhea patients who have diabetes is small, while the percentage of diabetic patients who have pyorrhea is large.

4. It is unwise for the dentist to attempt to diagnose diabetes by oral changes alone. The safest method is coöperation with a physician in making complete examinations, which, of course, include the appropriate study of the blood and urine.

5. With insulin and a controlled diet, the surgical procedures necessary to removing foci in the oral cavity can be undertaken with almost the same assurance as in the nondiabetic.

6. The elimination of these foci by the coöperation of the dentist and internist is not only safe but also may be the deciding factor in the case.

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IMMUNE TRANSFUSION IN LOBAR PNEUMONIA.

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In previous papers, a study was made of the rate of development of active immunity in normal animals and in patients with lobar pneumonia, following the intravenous injection of pneumococcus vaccine.[1,2] The present investigation is concerned with the production of passive immunity in normal men as a result of the intramuscular injection of pneumococcus vaccine, and the use of their blood in the treatment of lobar pneumonia. It was thought that the combination of type-specific pneumococcus antibodies plus uninjured complement present in normal human blood might be more influential in arresting a severe pneumonic infection than the use of horse serum, particularly in Types II and III. That whole blood from an homologous species would be of greater value than serum from a heterologous species was suggested by Tillett's results on pneumococcus Type III infection in rabbits.[3] The blood of normal individuals occasionally possesses small amounts of protective substances against one or more types of pneumococcus.[4] Of 10 donors in whom pneumococcus vaccine injections were begun, 3 of them had small amounts of type-specific protective substance in their blood before injection.

Methods. The donors were injected intramuscularly in the deltoid; occasionally the injection was made subcutaneously, in doses which varied from 1 to 25 billion organisms. The injections were given generally at weekly intervals, in some instances twice a week, over a period of time which varied from 6 weeks to 1 year. No general reactions were experienced by the donors, except in one instance when the patient became definitely feverish and suffered from considerable malaise 12 hours later. The arm was only slightly sore to the touch as long as the dose injected did not exceed 15 billion organisms. Blood was withdrawn from the donor at intervals to test the degree of protection which his serum had for mice.

Direct transfusions were done in all cases except one, the patient receiving from 1000 to 1600 cc. of blood in 2 to 3 transfusions within 24 hours.

The preparation of pneumococcus vaccine and filtrate is described in previous papers.[1,2]

Results. Eight patients with lobar pneumonia were treated by transfusion of blood from immunized donors. Five donors were employed. The degree of immunity present in the serum of the donor which was capable of passive transfer to mice varied considerably in each case. In no individual was the development of protective substance equal for each type of pneumococcus, even though equal amounts of each type of vaccine were administered. It is also true that patients with lobar pneumonia who were injected intravenously with vaccine made of 3 types of pneumococcus did not develop the same amount of protective substance for each type.[2]

The following table (Table 1) illustrates the response in the donor's serum after injection of pneumococcus vaccine over relatively long periods of time:

TABLE 1.—PROTECTIVE SUBSTANCE IN DONOR'S SERUM AFTER ACTIVE IMMUNIZATION.

Donor.	Survival after injection PN_1 culture plus 0.2 cc. donor's serum.			Survival after injection PN_2 culture plus 0.2 cc. donor's serum.			Survival after PN_3 injection of culture plus 0.2 cc. donor's serum.		
1	0.01	0.001	0.0001	0.01	0.001	0.0001	0.01	0.001	0.0001
	20	20	20	20	S	S	40	40	40
	20	20	40	20	S	S	40	40	S
	20	40	40	20	S	S	40	40	S
Controls: Dosage and death in hrs.	0.01	40 hrs.		0.01	40 hrs.		0.01	40 hrs.	
	0.001	40 "		0.001	40 "		0.001	40 "	
	0.0001	40 "		0.0001	40 "		0.0001	40 "	
	0.00001	40 "		0.00001	40 "		0.00001	40 "	
	0.000001	40 "		0.000001	40 "		0.000001	40 "	
	0.0000001	80 "		0.0000001	40 "		0.0000001	40 "	
	0.00000001	40 "		0.00000001	40 "		0.00000001	40 "	

REMARKS. Donor received intramuscular injections of pneumococcus filtrate and vaccine over a period of 12 months at approximately weekly intervals. Donor's serum showed no protection before injection.

The first donor (No. 1) received a total of 80 billion pneumococcus Type I, 170 billion of pneumococcus Type II, and 170 billion of pneumococcus Type III organisms. He also received 24 cc. of pneumococcus Type I and II filtrate. Injections were made intramuscularly at weekly intervals for a period of 12 months. It is seen in the table that he developed no protective substance against Type I that was marked enough to be shown in the protection experiments with mice. Since the culture injected to test immunity was not carried lower than 0.0001 cc., a degree of protection that was less than 1000 M.L.D. (minimal lethal doses) would not make itself apparent. In the case of Type II, the donor's serum protected against 10,000 M.L.D., and in the case of Type III against 1000 M.L.D.

In Donor 2 who received the same amount of vaccine over the same period, no protection developed in his serum for Type I or II, and only slight protection for Type III, 10 M.L.D.

In Donor 3, after a period of 6 weeks in which 87 billion pneumococcus Type II organisms, and 127 billion Type III organisms were injected, the donor developed only slight protection against Type III, but very marked protection against Type II, namely 100,000 M.L.D.

Donor 4 was injected for a period of 7 months, at approximately weekly intervals, receiving a total dose of 110 billion organisms of each type. He developed no protection for Type II, but marked immunity against pneumococcus Types I and III, equivalent to 100,000 M.L.D.

Donor 5 was injected intramuscularly for a period of 5 months, at first twice a week and later once a week, receiving a total of 100 billion organisms of each type. He developed no protection against Type II pneumococcus, but marked protection against Type I (100,000 M.L.D.) and against Type III (100,000 M.L.D.). No reason is apparent to explain satisfactorily why a donor will not develop protection against one type of pneumococcus and yet produce abundant antibodies against two other types.

TABLE 2.—PASSIVE IMMUNITY IN SERUM OF PATIENT BEFORE AND AFTER IMMUNE TRANSFUSION.

Case No., age and sex.	Transfusion of.	Survival after injection of pneumococcus Type III culture plus 0.2 cc. donor's serum.			
		0.01	0.001	0.0001	0.00001
1 Age, 58 Female	1000 cc. blood				
	Before	18 20 40	20 20 40	24 40 48	40 44 40
	5 hours after	8 8 8	40 8 8	8 8 8	8 8 8
	Control dosage Survival	0.001 40	0.0001 20	0.00001 40	0.000001 40

REMARKS. Patient had pneumococcus Type III in sputum, with sterile blood culture. She received 1000 cc. blood of Donor 5 in three doses in 24 hours. Treated in oxygen tent, 50 per cent oxygen, for 5 days. Recovered.

Case Histories. CASE 1.—(Table 2.) Female, aged 58 years. The patient took sick with a chill, fever, malaise and cough 3 days before observation. Cough became productive 2 days later of blood-tinged sputum. On the third day of illness she was only moderately dyspneic, without cyanosis, and appeared comfortable. Lung signs revealed consolidation of the right lower lobe. Temperature was 103.6° F.; pulse, 106; respirations, 24. The sputum contained pneumococcus Type III. The blood culture was sterile. On the fifth day of illness the temperature was 103.2° F.; pulse, 112; respirations, 32. Consolidation had spread to the

left lower lobe. She was now more dyspneic, cyanotic and prostrated. Oxygen therapy was instituted with an oxygen tent, and the patient was kept in 50 per cent oxygen for the following 5 days, with clearing of cyanosis and considerable relief of dyspnea. However, the patient continued to appear toxic and the temperature persisted. On the seventh day of disease two direct transfusions of 300 cc. each from Donor 5 were given. No change in the clinical condition of the patient occurred, and on the following day another transfusion of 400 cc. of blood was performed. On the following day (8 hours later) the temperature dropped once to 97.8° F., but then returned to its previous level, without any fall in pulse or respiration or improvement in toxemia or prostration. The patient continued to run fever and an elevated pulse and respiratory rate for 8 days thereafter, when the temperature became normal and the patient gradually convalesced.

The patient's blood before injection contained no protective substance against pneumococcus Type III, but 5 hours after the second transfusion her blood protected against 0.01 cc. of culture with a virulence of 10–6 or 10,000 M.L.D. Notwithstanding the fact that protective substances in considerable degree were introduced into her blood and were present 5 hours later, the patient continued to have a long-drawn-out pneumonia, with an elevated temperature which did not subside until 8 days later. Just how long protective substance was present in her blood is impossible to say as no further tests were made. The course of the disease indicates that they were soon used up and that convalescence was not established until her own immunity mechanism became active. The fact that the patient recovered does not appear, therefore, to have been dependent upon the transfusion of immune blood.

Case 2.—Male, aged 22 years. Following a cold, the patient became acutely ill 3 days before admission with cough, vomiting and pain in right chest. On examination he was acutely ill, with slight dyspnea. Lungs showed consolidation of the right lower lobe and right middle lobe. Sputum contained pneumococcus Type III, with blood culture sterile.

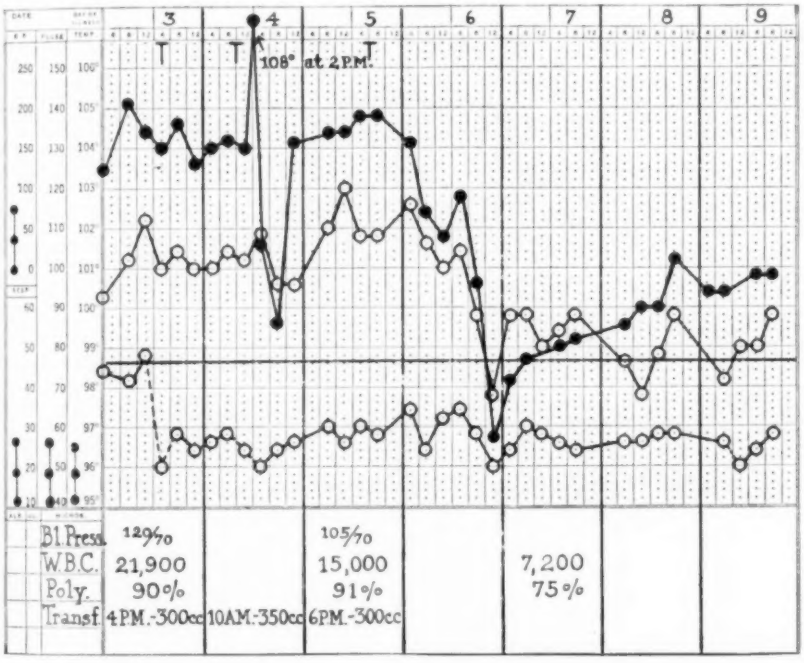
He was given an indirect transfusion of 300 cc. from Donor 5 on the third day of disease, without any reaction. On the next day an indirect transfusion of 350 cc. of blood was given which was followed by a severe chill, a rise in temperature to 108° F., a fall to 99.6° F. and a return to the previous temperature range of 104° F. No change in the clinical condition of the patient was apparent. On the following day, the fifth day of disease, the signs in the right lower lobe disappeared and consolidation of the right upper lobe appeared. A direct transfusion of 300 cc. of blood was then given without reaction, but without noticeable alteration in prostration or toxic appearance of the patient. The pulse rate assumed a higher level. The next day, the sixth day of disease, the temperature dropped to normal by crisis, with a corresponding fall in pulse and respiration and disappearance of prostration.

It was evident that no effect from any of the three transfusions was produced on the temperature, pulse and respiration (Chart I), or on the clinical appearance of the patient. The patient's serum contained protective substance after transfusion from the second to the sixth day of disease, although crisis did not occur until the sixth day. It is of interest that the course of the disease seemed uninfluenced by the presence of considerable amounts of Type III protective substance furnished by transfusion of immune blood.

Case 3.—Male, aged 19 years. Twelve hours before admission the patient became sick with epigastric pain, vomiting and malaise. On examination he was acutely ill, flushed, prostrated and lethargic. Lung signs indicated beginning consolidation in the left upper lobe. Sputum contained pneumococcus Type II. Blood culture on admission was sterile.

On the following day consolidation spread to the left lower lobe and blood culture was positive for pneumococcus Type II. A direct transfusion of 600 cc. of blood from Donor 1 was given, following a preliminary phlebotomy of 600 cc. The next morning a phlebotomy of 500 cc. was performed followed by a direct transfusion of 600 cc. of blood from the same donor. No change in the clinical condition of the patient was observed. Two days later a spread to the right lower lobe occurred and the patient became cyanotic and much more prostrated. Oxygen chamber therapy was instituted with 45 per cent oxygen. The blood culture continued positive 6 hours after the second transfusion and 1 day after the last transfusion, but was

CHART I.



sterile 2 days after the last transfusion. The fever persisted and did not reach normal until 7 days after the last transfusion, when the patient was definitely better, and oxygen therapy was stopped. (Chart II.)

As seen in Table 3, no protective substance was present in the patient's serum on the first and second days after transfusions totaling 1100 cc. of the donor's blood which contained considerable amounts of Type II protective substance. (Table 1.) On the fifth day, and on the seventh day after transfusion, when recovery was established, protective substance appeared in the patient's serum in large amounts, obviously related to the natural course of the disease. Immune transfusion appeared of no benefit for the following reasons: (1) The absence of protective substance in the patient's serum and the presence of a positive blood culture after transfusion of immune blood; (2) a spread of consolidation to the right lower lobe after both transfusions had been given; (3) persistence of fever and prostration for one week after transfusions.

CHART II.

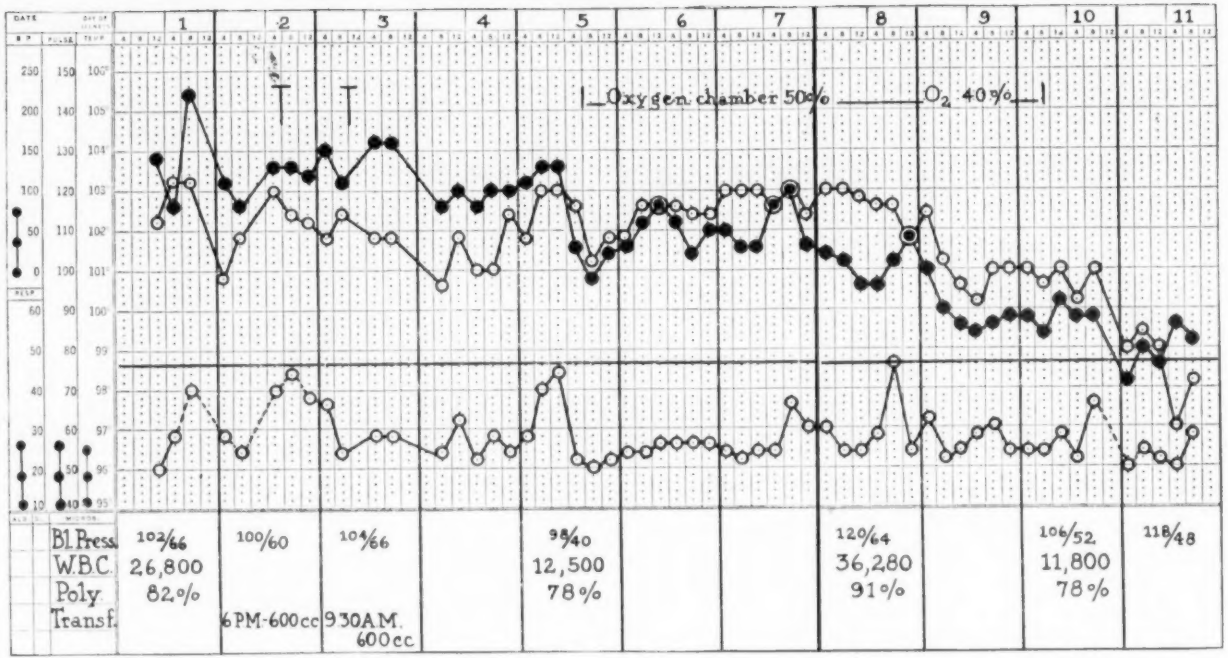

Oxygen chamber 50% ——— O2 40%
Bl. Press. 102/66 100/60 104/66 98/40 120/64 106/52 118/48
W.B.C. 26,800 12,500 36,280 11,800
Poly. 82% 78% 91% 78%
Transf. 6 PM-600cc 930 A.M. 600cc

TABLE 3.—PASSIVE IMMUNITY IN PATIENT'S SERUM BEFORE AND AFTER IMMUNE TRANSFUSION.

Case No., age and sex.	Day after transfusion.	Survival after injection of PN_2 broth culture plus 0.2 cc. patient's serum.			
		0.01	0.001	0.0001	0.00001
3 Age, 19 Male	Before	20	20 20 20	20 20 40	20 20 20
	First	20 20 20	20 20 40	20 20 20	20 40 40
	Second	20 20 20	20 20 20	20 20 20	20 20 40
	Fifth	20 20 20	40 50 8	8 8 8	8 8 8
	Seventh	20 40 8	8 8 8	40 40 8	20 60 8

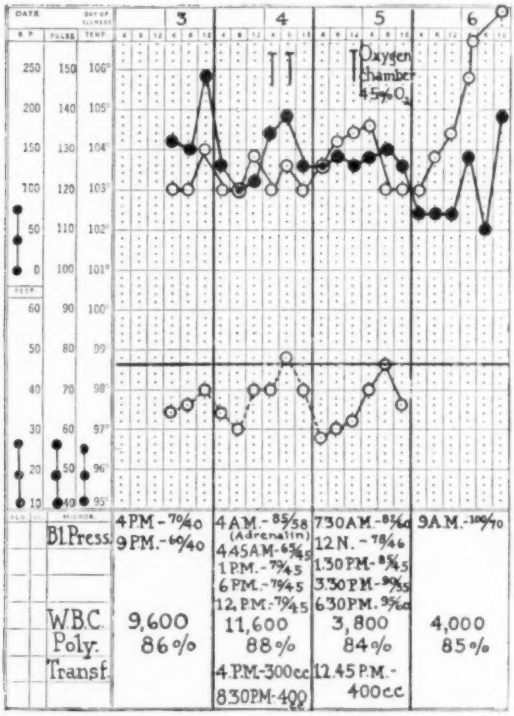
Controls:		
	0.01	20 hrs.
	0.001	20 "
	0.0001	20 "
	0.00001	40 "
	0.000001	40 "
	0.0000001	40 "
	0.00000001	40 "
	0.000000001	20 "

REMARKS. Patient had pneumococcus Type II in sputum with pneumococcus Type II bacteremia. He received 1100 cc. of blood of Donor 1 (see Table 1) in two doses in 16 hours. Blood culture persisted positive until two days after second transfusion. Treated in oxygen chamber, 45 per cent oxygen. Recovered.

CASE 4.—Male, aged 20 years. Twelve hours before admission the patient became ill with headache and pain in the left chest. On examination he appeared acutely ill and prostrated. Blood pressure was 70 systolic and 40 diastolic. Lung signs indicated beginning involvement of the left lower lobe. Two infusions of 500 cc. of 10 per cent glucose and stimulation by caffein sodium benzoate and adrenalin chlorid were given, with only temporary elevation of blood pressure to 85 systolic and 60 diastolic. Sputum contained pneumococcus Type II. Blood culture on day of admission was sterile, but on following day, the second day of disease, was positive for pneumococcus Type II. A direct transfusion of 300 cc. of blood from Donor 1 was given, followed in 4 hours by a transfusion of 400 cc. of blood from Donor 3 and 14 hours later by another transfusion of 400 cc. of blood from Donor 1. No improvement appeared to result from any of the transfusions. Blood pressure remained at 78 systolic and 46 diastolic. Blood culture persisted positive after each transfusion. Four hours after the last transfusion the blood count dropped from 11,600, polymorphonuclears 88 per cent to 3800, polymorphonuclears 84 per cent.

Signs of consolidation appeared in the right lower lobe, and cyanosis became marked. He was transferred to the oxygen chamber, oxygen concentration 45 per cent. Cyanosis began to diminish immediately, and the patient became much more comfortable. One hour after the patient was removed to the oxygen chamber blood pressure increased to 85 systolic and 45 diastolic, 3 hours later to 90 systolic and 55 diastolic and 5 hours later to 95 systolic and 60 diastolic. Quality of pulse was perceptibly fuller and firmer. On the following day the patient's condition was worse, a definite pericardial friction rub developed and that night he died. (See Chart III for clinical record.)

CHART III.



As seen in Table 4, no protective substance was present in the patient's serum after the first or third transfusion, even though the donors (Nos. 1 and 3) had developed considerable immunity against Type II pneumococcus.

The patient was seen in the first day of disease and treated on the second day with three transfusions of immune blood. No clinical improvement resulted, however, either in the signs of vasomotor shock, the disappearance of the positive blood culture or in the prevention of spread of the pulmonary lesion. The absence of any carry-over of protective substance from the donor suggested that the overwhelming toxemia quickly exhausted all the protective substance injected. The inhalation of 45 per cent oxygen was temporarily beneficial in increasing his comfort, as well as in terminating the signs of vasomotor shock, *i. e.*, raising the blood pressure and increasing the volume and tension of his pulse.

TABLE 4.—APPEARANCE OF PROTECTIVE SUBSTANCE IN PATIENT'S SERUM BEFORE AND AFTER IMMUNE TRANSFUSION.

Case No., age and sex.	Day after transfusion.	Survival after injection PN_1 culture plus 0.2 cc. patient's serum.			Survival after injection PN_2 culture plus 0.2 cc. patient's serum.			Survival after injection PN_3 culture plus 0.2 cc. patient's serum.		
		0.001	0.0001	0.00001	0.001	0.0001	0.00001	0.001	0.0001	0.00001
4 20 years Male	Before	30 30 30	30 30 30	30 30 30	35 35 35	35 35 35	35 35 35	35 35 40	40 40	40 40
	5 hours after first transfusion	30 30 30	30 30 30	30 30 30	35 35 35	35 35 35	35 35 35	40 40 40	40 40 40	40 40 40
	12 hours after third transfusion	30 30 30	30 30 30	30 30 30	30 30 30	30 30 30	30 30 30	30 30 30	30 30 30	30 30 30
	Controls:	0.000001 30 hrs. 0.0000001 30 " 0.00000001 30 " 0.000000001 30 "			0.000001 30 hrs. 0.0000001 30 " 0.00000001 30 " 0.000000001 30 "			0.000001 40 hrs. 0.0000001 40 " 0.00000001 40 " 0.000000001 40 "		

REMARKS. Patient had pneumococcus Type II in sputum and blood culture. He received 1100 cc. of blood mostly of Donor 1 (see Table 1) in 24 hours. Blood culture persisted positive after each transfusion. Treated in oxygen chamber, 45 per cent oxygen. Died.

CASE 5.—Male, aged 35 years. The patient was seized with a chill, followed by fever, cough and bloody sputum 6 days before observation. He became steadily worse, and on the sixth day was prostrated and toxic, markedly dyspneic and cyanotic. Lungs showed consolidation of the right middle and lower lobes and the left lower lobe. Sputum contained pneumococcus Type III. Blood culture was positive for pneumococcus Type III. Temperature was 105° F.; pulse, 140; respirations, 50.

He was put in an oxygen tent with 50 per cent oxygen, with diminution in cyanosis and a decrease in pulse rate. Three transfusions of 400 cc. each were given in 24 hours from Donor 4. No improvement in his clinical condition was observed and 12 hours later the patient died.

The blood culture before and after the first two transfusions was positive, but 2 hours after the last transfusion was sterile. However, no protective substance was present either before the transfusions or after 1200 cc. of immune blood were given.

The patient seemed fatally ill when first seen. The treatment by transfusion of immune blood did not appear to change the clinical condition of the patient in any way. His blood retained none of the protective substance introduced when tested two hours after the last transfusion.

CASE 6.—Male, aged 36 years. The patient became sick 4 days before observation, with chill, fever, cough and bloody sputum. On examination on the fourth day he was markedly prostrated, toxic, dyspneic and cyanotic. Lungs showed consolidation of the right lower lobe and the left lower lobe. The sputum contained pneumococcus Type III. Blood culture was positive for pneumococcus Type III. The patient was placed in an oxygen tent with 50 per cent oxygen, and three transfusions totaling 1200 cc. of blood were given in 24 hours from Donor 4. No change in the clinical condition of the patient took place, and on the following day he died.

Blood culture persisted positive after all transfusions. No protective substance was present for pneumococcus Type III before or 3 hours after the third transfusion. The injection of immune blood did not alter in any way the progressively fatal character of the infection.

CASE 7.—Female, aged 40 years. The patient took sick, with chill, fever, cough and bloody sputum 48 hours before observation. On examination she was prostrated, toxic, dyspneic and cyanotic. The lungs showed consolidation of the right lower lobe and beginning involvement of the left lower lobe. The sputum and blood culture both contained pneumococcus Type III. The patient was treated in an oxygen tent with 50 per cent oxygen, with considerable relief temporarily, decreased cyanosis, lower pulse and increased comfort in breathing. She was given 1000 cc. of blood in two doses from Donor 5 and 600 cc. of blood from Donor 4. However, her condition was unchanged on the following day in respect to temperature, prostration and toxic appearance of the patient, and on the second day after the last transfusion the patient died.

The blood culture remained persistently positive, and six hours after the last transfusion the patient's serum contained no protective substance against pneumococcus Type III. Although the patient was treated early in the disease, no effect was produced by relatively large transfusions of immune blood.

CASE 8.—Male, aged 61 years. The patient became ill 36 hours before admission, with chill and pain in the right chest. Examination revealed an elderly man acutely ill. The lung signs indicated consolidation in the left lower lobe, with scattered crepitant râles in the right lower lobe. The sputum contained pneumococcus Type III. Blood culture was sterile on the day of admission, positive for pneumococcus Type III on following day. Despite the use of digitalis, auricular fibrillation began the day after admis-

sion. A phlebotomy of 500 cc. of blood was performed on the day after admission followed by a direct transfusion of 600 cc. of blood from Donor 4. Eight hours later a second direct transfusion was given from Donor 2. No clinical improvement resulted, the patient became steadily weaker and died the next day.

No protective substance was present in the patient's serum on the day following the two transfusions totaling 1200 cc. of blood. Blood culture persisted positive. The patient was a poor subject, but no betterment resulted from the transfusions of immune blood.

Discussion. Of 8 patients who were treated by immune transfusion, 6 were due to pneumococcus Type III and 2 to pneumococcus Type II. Four of the 6 Type III cases had a bacteriemia and all died. The 2 Type III cases with sterile blood culture survived. Of the 2 cases of Type II pneumonia with positive blood culture, 1 died and 1 survived.

The immediate effect of the transfusion on the clinical condition of the patient was negligible. No lessening of toxemia, prostration, cyanosis or dyspnea was observed. In four fatal cases, the blood culture was not rendered sterile, nor was the spread of pulmonary consolidation checked. The determination of protective substance in the patient's blood before and after transfusion of immune blood showed an absence of the introduced protective substance in all the 5 fatal cases. Of the 3 who survived, 1 showed no protective substance in his serum until 2 days following the last transfusion, which therefore could not be ascribed to the introduction of immune blood. In 2 cases of pneumococcus Type III infection with sterile blood culture, the patient's serum contained protective substance after immune transfusion although not before. Their clinical course, however, was so long drawn out that it would not be possible to ascribe recovery to the protective substances introduced by transfusions.

Conclusions. 1. Eight patients with pneumococcus lobar pneumonia, 6 due to Type III and 2 due to pneumococcus Type II, were treated by transfusion of 1000 to 1600 cc. of blood from donors immunized over long periods of time.

2. No favorable effect was observed on the clinical condition of the patient as a result of any of the transfusions. The introduction of protective substance present in the donor's blood could not be demonstrated in the patient's blood in the 5 fatal cases and appeared to have no influence on the course of the disease in the 3 recovered patients.

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THE CHOLAGOGUE EFFECT OF THE INTRAVENOUS INJECTION OF SODIUM DEHYDROCHOLATE, WITH A RÉSUMÉ OF LITERATURE ON BILE SALT METABOLISM.*

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Before we report the results of our study as to the cholagogue effect of sodium dehydrocholate, we feel it important that a review of the literature bearing on the physiology of bile salt metabolism and its influence on bile output should be discussed for the following reason: Any study such as the one here reported is of limited value unless all of the factors as hereafter discussed are taken into consideration and suitably controlled. We acknowledge that, save for adopting a standard preliminary diet for one meal before testing the cholagogue effect of sodium dehydrocholate, we have not adhered to the criteria which we now believe important and which should be utilized in further cholagogue and choleretic clinical studies.

Bile Salt Metabolism. Bile has as its more important and recognized constituents bile salts, bile pigments, cholesterol, certain inorganic salts and water.

Bile salt metabolism and the hepatic biliary secretory mechanism is fundamentally involved in the discussion of any phase of the cholagogue activity or the choleretic action of any drug or group of drugs.

Cholagogue action has to do with volume of bile output without regard for the quantitative amounts of the various constituents, while choleretic action has to do with the quantitative amounts of the individual biliary constituents other than water. The importance of distinguishing between these two types of hepatic activity becomes obvious when considering bile secretion and the factors governing it.

The anabolic phase or constructive portion of this complex metabolism is today an unknown process. It necessarily involves the origin and formation of the precursor substances and their collection and transmission to the hepatic epithelial cell, which is believed to be the seat of bile salt synthesis. Regarding the precursor substances themselves nothing is known. The catabolic or destructive phase involving the destruction of excess bile salts also remains obscure.

* Presented in part before the Thirty-fourth Annual Meeting of the American Gastro-enterological Association at Atlantic City, N. J., May 5, 1931.

As in other complex metabolic systems in the human body, may we not suppose that a regulatory mechanism governs the anabolic and catabolic phases of bile salt metabolism (and subsequent bile secretion), because we are cognizant of the fact that the bile salts in themselves are the chief and practically the sole bile secretory stimulants.[2] Such a regulatory mechanism has been suggested by the investigators in the field of bile salt metabolism.

Regarding the elimination of bile salts, the only outlet recognized at the present time is the bile itself. Throughout this paper the terms bile salts and bile acids are used interchangeably.

Bile salt metabolism and concomitantly bile salt and bile production are theoretically influenced by three major factors: (1) Exogenous, embracing principally foods and drugs; (2) endogenous, embracing principally the effects of endocrine glandular secretions and endogenous nitrogen or protein metabolism; (3) the enterohepatic factor. A consideration of these factors and their relation will be attempted, especially as brought out by the work of Whipple and his colleagues, which is outstanding in this field.

Whipple and Smith,[1] working with dogs in a study of bile salt metabolism, found that on a given diet of salmon and bread there is a definite level of bile salt output per kilo of body weight during 24 hours. If to these bile-fistula dogs their entire 24-hour output of whole bile is added to the salmon-bread diet a rise in the bile salt output occurs at a higher plateau-like level. Whereupon, if additional or supplementary bile feeding is now added there occurs a further rise to a higher level of output; if this supplementary feeding is withdrawn there is a prompt fall back to the previous plateau-like level. Furthermore, when very large doses of bile salts alone are given only a part is eliminated in the bile and the fate of the bile salt is unknown. Due consideration is taken of the possibility that small amounts of bile salt escape in the urine and that, although the feces become dark in color with some diarrhea with heavy bile salt feeding, accurate quantitative determination of bile salts in the feces has not thus far been found possible. Thus it appears that the body can eliminate in the bile only a certain amount of the bile salt and the disposition of the excess is unknown. It is further shown that within certain limits quantitative absorption of bile salts from the intestine and resecretion by the liver is true, and this fact plus a constant endogenous as well as exogenous production day by day would soon lead to an absurd excess body content or, as Whipple aptly puts it, "the dog would soon become a pillar of bile salts."

Obviously there must be some sort of a regulatory mechanism by which a balance is maintained in this much overlooked phase of body physiology. Smith, Groth and Whipple[2] observed that the bile salt secretion in dogs in spite of a single daily feeding was quite uniform during the 24 hours. Considering the three 8-hour

periods, beginning at 8 A.M., the bile salt output was practically the same except for the night period embracing the time of bodily rest, when it was slightly lower than for the evening period, representing the period of maximal digestive activity. Therefore, this so-called base line level of bile salt output is rather uniform for a given dog on a salmon-bread diet. In addition, the institution of sugar feeding or fasting following the salmon-bread diet resulted in a gradual fall in bile salt output during the following 2 or 3 days; resumption of the salmon-bread diet then called forth a rise in output over a period of 2 or 3 days to the previous salmon-bread level. This gradual rather than abrupt fall and rise respectively following changes in the diet suggests a storage of the precursor substances incident to bile salt synthesis to be gradually utilized as fasting continues, and when a favorable diet is resumed suggests a storage of the precursor material to be utilized when an emergency need arises. Wisner and Whipple[3] again corroborated the above findings. They determined the bile salt output during four 6-hour periods, and results showed a remarkably uniform level for each period. Greene, Rowntree, *et al.*[4] observed bile acid secretion in the bile of bile-fistula dogs for 30-minute periods following the oral administration of bile acids and found little change during the first 30-minute period, but thereafter a striking increase in the bile acid output occurred during the second, third, fourth and fifth 30-minute periods, corresponding in part to the volume of bile.

The Rôle of Hepatic Epithelium. The hepatic epithelial cell probably plays an important rôle in the secretion of bile salts and of bile itself. To it has also been ascribed the function of synthesis of the bile salt molecules, although definite proof is lacking. Concerning the hepatic epithelium with its highly complex physiology little is known. Its internal or intracellular metabolism and its relation to bile salt synthesis and secretion are obscure. However, in the final analysis, and in the face of our ignorance of the origin and formation of the precursor substances of bile salt construction, and in spite of our lack of knowledge concerning the seat of bile salt synthesis and bile salt destruction, we should assign to the hepatic epithelial cell an important rôle in bile secretion and bile salt metabolism upon the few facts elicited by the investigations in this particular field.

Cramer and Ludford[5] conclude from their study on the cellular mechanism of bile secretion and its relation to the Golgi apparatus of the liver cell, in which they utilized the livers of mice, rats and guinea pigs both normal and pregnant, that the bile constituents appear in the Golgi apparatus of the liver cell which in the process of bile secretion first enlarges and then fragments. The fragments are dispersed throughout the cytoplasm and upon reaching the periphery pass their contents into the intercellular bile capillaries.

The possibility that the intrahepatic portion of the enterohepatic

circulation of bile salts exerts an influence on the internal metabolism of the hepatic epithelial cell, which is essentially concerned in many vital processes, has been suggested.[1]

A stimulatory action on the liver cell has been ascribed to tryptophane,[6] isatin and even indigo, in view of the marked cholagogue effects of these substances, despite sugar feeding which in itself brings about marked diminution of volume and extreme concentration of the bile. A relationship between bile salts and the above stimulative substances is suggested because of their similar effects on the hepatic epithelium.

Chloroform and phosphorus have long been recognized as liver poisons. Smyth and Whipple[7] administered small doses of chloroform by inhalation and by stomach tube to dogs and found a marked reduction in bile salt output, to 10 per cent of normal or even less. Associated with these small doses of chloroform there was a functional depression of the liver cell, but no actual liver cell injury or organic change could be demonstrated. Phosphorus, even in lethal doses, does not seem to produce the marked diminution in bile salt output that is caused by small doses of chloroform, even though organic injury to the liver cells may be present in the phosphorus poisoning.

The metabolic activity of the hepatic epithelium has been found by Greene and Rowntree[4] to be disturbed in dogs following operative removal of the gall bladder, under amytal narcosis, with cannulization of the common duct, with coincident depression of the bile salt secretion. The liver bile collected for a period of 6 hours after introduction of bile salts into the duodenum of the animal, following such an operative procedure, showed a lessened bile salt output. This apparent disturbance of hepatic intracellular metabolic activity and depressant effect upon bile salt secretion was probably due either to the operative procedure itself, to the anesthetic used, or to disturbances in the portal circulation. The functionally deficient liver,[8] such as one with an Eck fistula, secretes less than half the normal amount of bile salts on a standard diet during a definite period. This, therefore, offers an additional link in the chain of evidence pointing toward the liver cell as the center of bile salt synthesis.[9]

Bile secreted against an abnormally high pressure, such as that existing in partial obstruction of the common bile duct, contains less amounts of the biliary constituents, such as bile salts, bile pigment and cholesterol. The probable mode of action seems to be a depression of the functional activity of the liver cells.

The protective influence on hepatic epithelium,[10] exerted by certain dietary factors, such as sugar and those diets which are rich in carbohydrates, and the parenchymatous organic foods, such as liver and kidney, against damage by chloroform poisoning seems to have been established. The feeding of these specific dietary

substances to dogs prior to chloroform administration seems to protect the liver cell from injury, probably by virtue of some adjustment or change in the cellular metabolism itself, rather than because of substances circulating in the blood stream.[11]

Proteose intoxication is associated with a characteristic symptomatology, together with a profound disturbance in the endogenous nitrogen metabolism yielding increased nitrogen and increased blood nonprotein nitrogen, indicative of considerable body protein catabolism. Bile salt production is reduced as a result of proteose intoxication, probably as a result of hepatic epithelial cell injury, functional in type, since there is no evidence of histologic change. This offers a further confirmatory fact in the localization of bile salt synthesis in the liver cell.

Exogenous Factors. The exogenous factors which influence bile salt metabolism and subsequently bile salt production and bile secretion are principally dietary. In the dog it has been demonstrated[8,12,13] that food protein is of foremost importance in the determination of the level of bile salt output. Meat and meat products cause a pronounced increase in the bile salt output. Alcoholic extractives of meat have no effect on bile salt output, although the residue loses none of its power of increasing production. Commercial beef extracts may contain some elements causing increase in bile salt production. Yeast nucleic acid is not effective in changing bile salt output. Lipoids and cholesterol when fed to dogs yield no change in bile salt secretion.

The various dietary factors may influence principally the volume of bile or the content of any of the bile constituents. In our present discussion, however, we are concerned with the volume of cholagogue effects, and the bile salt secreted is considered the most potent cholagogue factor known.

Okada,[14] working with bile-fistula dogs found that raw egg white, boiled egg white, fat, oil, soap solution, acids, Witte's peptone, meat extractives and bile salts or bile itself introduced into the stomach caused an increase secretion of bile. Whereas he found that pure cane sugar, cakes baked of starch and sugar, and water had no effect on the bile secretion when introduced into the stomach. Whipple, Smith and Smyth[6,13] found that tryptophane occupies a unique place among those substances influencing the secretion of bile. Gelatin feedings in bile-fistula dogs results in bile salt production at a lower level than that of salmon-bread diet. This observation suggests the possibility that one of the amino acids not present in gelatin plays an important rôle in bile salt production and bile secretion. Gelatin plus tyrosin yields no effect. Gelatin plus tryptophane immediately raises bile salt output to slightly below the maximal values obtained on a meat diet. This observation would lead one to ascribe the determining rôle to tryptophane, but on a tryptophane plus sugar diet no increase in

bile salt output occurs. The conclusion may be that there is some other substance in gelatin plus tryptophane necessary to raise bile salt output. This cholagogue result of gelatin feeding shows a definite fall from day to day, more so than the fall in bile salt output on gelatin plus tyrosin and gelatin plus hydroxyphenylglycin diets. Cholagogue action is markedly increased on a gelatin plus tryptophane diet, slightly more on a tryptophane plus salmon-bread diet with coincident rise in bile salt output. Resumption of fasting and sugar feeding reduces bile salt output to near the fasting base line level. Tryptophane given now with sugar feeding results in a fall to the base line level. This suggests that tryptophane alone is inefficient in influencing bile salt secretion. Resumption of a salmon-bread diet now results in a rapid and unusually high output of bile salts, which suggests some influence of the preceding tryptophane feeding. Tryptophane plus sugar feeding yields a notable cholagogue result but no increase in bile salt output, which is in marked contrast to sugar feeding alone which produces extreme bile concentration. Tryptophane, isatin and even indigo added to the diet of dogs cause a conspicuous cholagogue effect, suggesting an influence on the hepatic epithelium separate and distinct from the bile salts as factors in bile secretion, or these various factors may be interrelated.

Bile salts themselves definitely influence bile salt secretion and bile secretion. Wisner and Whipple[3] found that the oral administration of taurocholic acid in bile-fistula dogs results in a marked rise in bile salt output during the first 6-hour period and a return to a normal level in the second 6-hour period. However, the cholagogue effect is still marked during the second period, indicating dissociation of bile volume from bile salt output. The appearance of bile acids in the bile is delayed and their secretion prolonged when administered by mouth,[4,15] in contrast to the prompt appearance and secretion when administered intravenously. Approximately the total quantity of bile acids injected intravenously was recovered in the bile within 2 hours after administration. Bile acids are eliminated rapidly[15,16] after administration with even maximum dosages compatible with recovery of the animal and their concentration in the blood stream persists for only 1 or 2 hours.[16] Bile or bile acids by oral administration result in an increase in the bile acids in the portal vein while the amount in the systemic circulation is unchanged.[17] Injection of bile into the duodenum results in an increased pancreatic secretion as well as increased flow of bile. Similar introduction of bile into the ileum causes increased flow of bile with no effect on pancreatic secretion, as follows the intravenous administration of bile salts. Although the intravenous injection of purified secretin causes a marked flow of pancreatic juice and augments the flow of bile, it is believed that this effect is secondary and is dependent upon its prior action on

the pancreas with the products of pancreatic metabolic activity then passing into the portal blood and thereby stimulating bile secretion in the liver.

The enterohepatic circulation of the bile salts notably influences the secretion by the liver, quantitative absorption from the intestine and resecretion by the liver. It is an omnipresent factor to be considered in the metabolism of bile salts and also in secretion of bile volume as well as quantitative bile salt elimination. A regulatory process is undoubtedly present to maintain a balance between anabolic and catabolic phases of bile salt metabolism.[18] Unfortunately mystery still enshrouds this important stablizing mechanism.

Drugs have long been supposed to possess cholagogue powers. Smyth and Whipple[19] found that calomel, hydrochloric acid, sodium salicylate and ethyl alcohol show no constant effect on bile secretion or bile salt output. Atropin and pilocarpin likewise cause no observable change in the bile secretion. Phlorizin and quinin are similarly powerless in this respect. Hemoglobin[18] injected intravenously produces no change in bile salt output. The salicylates[18] have never produced constant change in bile salt output. Okada,[14] working with bile-fistula dogs, found that the following drugs increase the flow of bile, namely, sodium salicylate, salol, chloral hydrate, cream of tartar and alcohol. Atropin produces a slightly lessened flow and pilocarpin a slightly increased flow of bile. Nicotin results in an inconstant increase in bile secretion. Calomel is without effect on bile flow.

Vigorous exercise[20] exerts no effect on the bile flow. Hot weather depresses markedly the flow of bile in dogs, although the animals remain in good general condition. Intercurrent diseases unassociated with jaundice exert a marked depressant effect on bile secretion, in fact the flow may almost cease. It is quite interesting to note that in the presence of these conditions the bile secretion is unaffected by the oral administration of the best cholagogue, namely, bile itself. This suggests that bile or bile salts act most favorably when the dog is healthy, the weather not too oppressive and the food intake sufficiently abundant and proper. Operative procedures[18,20] on the gall tract result in a scanty bile secretion for the first few days postoperatively, and not until 7 to 10 days after operation does the bile resume its usual appearance. In dogs under amytal narcosis and operative gall tract procedures[4] there was a notable diminution in bile output by the liver following the operation. In the presence of an abnormally high pressure,[9] such as occurs in partial obstruction of the common bile duct, there results a greater decrease in the amounts of total bile constituents than in the volume of bile secretion.

Endogenous Factors. The endogenous factors which influence bile salt metabolism are apparently closely associated with body protein metabolism. The base line level of bile salt output in the

fasting dog is a fairly constant one and remains unchanged during long periods of fasting.[2] This suggests that bile salt secretion represents the endogenous portion of bile salt metabolism and is probably the result of body protein breakdown. Whipple's work[18] suggests very definite relationship between body protein metabolism and bile salt metabolism. An interesting parallelism[12] exists between bile salt output and urinary nitrogen, namely, in fasting and sugar feeding there is low bile salt output and low urinary nitrogen, while in high meat diets a high bile salt output occurs, with a high urinary nitrogen. This suggests that body protein or food protein is the source of an essential precursor substance in bile salt synthesis.

The influence of the secretions of the endocrine glands on bile and bile salt secretion is noteworthy. Downs and Eddy[21] found that secretin increases the amount of bile secreted. Adrenalin depresses the amount of bile as do mammary, orchic, ovarian, pancreatic and thymic gland substances. Spleen and thyroid gland substances do not affect the amount of bile secreted in a constant or definite manner in cats. The effects of thyroid substance and thyroxin[11] on bile secretion or bile salt production in dogs are negative. Mellanby[17] believes that secretin is not primarily a cholagogue, but increases the flow of bile by virtue of its stimulus to pancreatic activity. The resultant metabolic products are passed into the portal blood stream and thence to the liver, where they excite hepatic activity which results in an increased secretion of bile. Downs[22] and also Okada[14] corroborated the views of Downs and Eddy[21] and of Mellanby[17] as regards the influence of certain endocrines on bile secretion.

Enterohepatic Factors. The enterohepatic factor concerns the secretion of bile salts by the liver cells, their discharge into the duodenum in the bile flow, their reabsorption by the intestinal mucosa into the portal circulation and their subsequent resecretion by the liver cells. This is the so-called enterohepatic circulation of bile salts and is, therefore, definitely related quantitatively to the exogenous and endogenous factors as previously discussed.

In addition some discussion should be given to bile salt synthesis or the anabolic phase of bile salt metabolism. What follows represents the comparatively little that is now known of this complex physiology.

Bile Salt Synthesis. Cholic acid[23] appears to be the limiting factor in bile salt metabolism. Taurin is thought to be available in excess in the body for union with any newly formed cholic acid radicals present, thus yielding taurocholic acid. Cystin seems to be the source of most of the taurin. It has been suggested by Foster, Hooper and Whipple[23] that the indol ring of indigo and isatin is probably utilized by the body to synthesize cholic acid. A strong physiologic action between taurin and cholic acid appears to exist in the body.

During full diet periods taurin seems to be more abundant in the body for linkage with cholic acid than during the fasting periods, or at least it is more available. Cholic acid seems to have no physiologic relationship to cholesterol and apparently cholesterol has no influence over cholic acid metabolism, because cholesterol when fed alone or combined with taurin has no influence on bile acid secretion.[23] Furthermore, terpene hydrate or camphor fed alone or in combination with taurin has no influence on bile acid production. Red blood cells fed alone or hemolyzed and injected intravenously have no effect on bile acid secretion.

Foster, Hooper and Whipple[8] further found that the bile acid output in a fistula dog following a long fasting period will not react to the usual high level on the resumption of a high-protein diet. This fact suggests the utilization of precursor substances of bile acid formation in some other body process, such as the supplying of some important substance relative to body protein which has been depleted during the fasting period. Whipple[18] again points out some very interesting facts concerning bile salt synthesis. He states that the taurin of taurocholic acid and the glycocoll of glycocholic acid are amino acids, both of which are present in the body. Glycocoll may be formed within the body and taurin is probably in large part from the cystin of the food or body protein. Taurin and glycocoll are probably present in excess in the body under modern conditions and are available for bile acid formation. Cholic acid is the key substance of bile acid synthesis and is, therefore, the limiting factor in its formation. The origin of cholic acid is unknown, nor is anything known of its catabolism or its elimination other than by way of the bile excretion. It is a complex substance containing no nitrogen, and has been assigned a relationship to turpentine and camphor. Taurin itself administered intravenously exerts no effect on bile acid secretion. Taurin and cholic acid by mouth have the same effect on bile acid secretion as taurocholic acid orally administered, both of which increase bile acid production. Taurin given intravenously and cholic acid given by mouth cause increased bile acid output. These facts suggest a very strong physiologic relationship between these substances in the body tissues.

An additional fact showing the importance of taurin in the synthesis of bile acids occurs when cholic acid is fed to dogs. During long fasting periods a minimal output of bile acids results; but if cholic acid is fed during full diet periods it yields a maximal output of bile acids. This observation is evidence of the available supply of taurin which was low during fasting and high during full diet periods.

Greene, Aldrich and Rowntree[16] suggest that a probable failure of bile acid synthesis occurs after the first few weeks of experimental jaundice produced by obstruction of the common bile duct, because they find that the bile acid content of the blood increased rapidly

immediately following the onset of obstruction, then decreased during the first few weeks of jaundice and finally tends to return to a normal level. In addition, they find the rate of elimination of bile acids administered intravenously to be greatly delayed in the presence of experimental jaundice.

Finally, as a preliminary to our study of an alleged nontoxic bile salt it is necessary to review some points in regard to the toxicity of bile salts and their therapeutic application.

The Toxic Factor in Bile. Bile has long been known to be markedly toxic to human tissues. The effects of bile peritonitis with its severe toxic manifestations and usually fatal result are well known among investigators and surgeons. The use of intravenous bile salts, such as sodium taurocholate and glycocholate, as well as whole bile solutions, is attended with marked toxic reactions even in relatively small doses.

The cholates,[24] and therefore inferentially the bile salts, occupy a far more important position in the normal, as well as diseased, economy than the other biliary constituents. Furthermore, the bile salts are undoubtedly the most injurious factors in biliary disturbances. The effect of diversion of bile[25] into the systemic and portal circulations, by anastomosis of the common bile duct and gall bladder with branches of the portal vein and vena cava, resulted in the death of the animals with such portal anastomosis in from 3 to 7 days and in animals with systemic venous anastomosis in from 18 to 48 hours.

Determination of the toxicity of purified bile preparations resulted in the conclusion by Still[26] that the cholate radical is responsible for the toxicity of bile. Further, as determined by intravenous administration in the dog, by intraperitoneal administration in the rabbit and by intralymphatic administration in the frog, the order of toxicity of the naturally occurring bile salts is: (1) Cholic acid; (2) desoxycholic acid; (3) glycocholic acid. Also, that bilirubin is a nontoxic substance and that the bile acids are the most toxic substances in the bile.

Horrall and Carlson found that the intravenous administration of whole gall bladder bile from one dog to another is dependent upon the amount of bile injected and the rate of injection.[27] Death of the dogs resulted from small amounts of the whole bile injected rapidly, while larger doses slowly administered produced only transient symptoms. However, in spite of the fact that early death does not result from such injections, the dogs appear to have a marked lowering of their resistance to infection, notably pneumonia. These authors suggest that the bile salts may cause dissolution of the limiting membrane of tissue cells, may change their surface tension and may destroy the normal cellular metabolism. Furthermore, bile injected in sufficient quantity to be fatal in 24 hours is not modified in its toxic effects by the presence of bacteria.

The toxicity of bile is unaffected by boiling or freezing. The dialyzable portion of whole bile possesses the same degree of toxicity as whole bile, while the nondialyzable portion possesses no element of toxicity. The cholate radical is the toxic portion of the bile salts, such as sodium taurocholate and sodium glycocholate; the absence of any toxic element in bilirubin is again corroborated.

The results of a study by Macht and Hyndman[28] of the relations between the chemical structure of bile acids and their reactions on plants and animals showed that the taurin radical of sodium taurocholate and the glycin radical of sodium glycocholate possess no toxicity toward plant and animal protoplasm; that cholic acid exerts a marked depressant effect on the neuromuscular and cerebrospinal reactions of rats operating in the circular maze; that the cholic acid exerts a marked depressing effect on the growth of seedlings; that the toxic manifestations of bile acids on animal as well as plant protoplasm are attributable to the cholic acid portion of the bile salt molecules. The effect of sodium taurocholate on the permeability factor of tissues has been shown by Osterhout[29] to decrease it, and it, therefore, suggests a possible antagonism to the effects of sodium chlorid and other substances, which thus increase the permeability factor in tissues.

Nontoxic Bile Salts. Thus it may be seen that the use of sodium taurocholate and sodium glycocholate orally and to a considerably greater extent intravenously was a highly perilous procedure in human beings because of their extremely toxic action. Nontoxic bile salts preparations have long been sought that they might be used as cholagogues and choleretics in the treatment of hepatic and biliary tract disease.

Neubauer and Pohl,[30] working in different laboratories, both found that apocholic acid, desoxycholic acid, dehydrodesoxycholic acid and dehydrocholic acid were the only bile acids of the whole group under investigation which had a definite secretion-stimulating action. Rabbits were used as the experimental animals because of the extraordinary regularity of their bile secretion. Neubauer and Adlersburg[30] demonstrated that a greater flow of bile followed the administration of dehydrocholic acid than occurred following the giving of cholic acid. Furthermore, the toxicity of dehydrocholic acid has been shown to be minimal (1) by virtue of its extremely slight hemolytic effect; (2) because of its minimal toxic effect on the isolated heart of a frog, showing it to be one-twenty-fifth as toxic as desoxycholic acid; (3) by virtue of its increased tolerance in relatively large doses by the body as a whole. The maximum nonfatal dose is 100 times that of desoxycholic acid and 11 times that of sodium taurocholate.

Neubauer[31] also found that the administration of dehydrocholic acid to human beings by the intravenous method has demonstrated that there is a striking increase in the quantity of bile secreted;

that the specific weight and relative and absolute dry residue of the bile increased, and that the viscosity tends to increase. Furthermore, the use of the sodium salt of dehydrocholic acid as a choleretic was confirmed by Wakefield, Powelson and McVicar,[32] who found that it definitely caused an increased flow of bile in 18 out of 20 human patients studied.

With this preliminary discussion of the literature, we now proceed to report the results of a clinical study of the cholagogue effect of the alleged nontoxic sodium salt of dehydrocholic acid.

Clinical Study of Sodium Dehydrocholate. Dehydrocholic acid was first introduced into therapeutics by Adlersberg and Neubauer in 1925. It occurs as a fine, crystalline, colorless powder, forming needle-shaped crystals and having a melting point of 233° C. The sodium salt of dehydrocholic acid, known as sodium dehydrocholate (trade name, Decholin-Sodium), is readily soluble in water, less readily in alcohol, producing a weakly alkaline solution having a bitter taste. Dehydrocholic acid is produced by oxidizing cholic acid.

Purpose of Study. Our present investigation was made to determine only the cholagogue or volume effect following the intravenous administration of sodium dehydrocholate. We realize the difficulties and probable criticism of the duodenal collection of biliary secretion and its source of error especially in quantitative volumetric determinations. We are cognizant of the fact that the external secretion of the pancreas is poured into this area; that the duodenal secretion is present; that gastric secretion is intermittently entering the duodenum. Therefore, accurate quantitative estimation of biliary secretion has been impossible. However, observations of the physical characteristics and color changes in the bile made during the study lead us to conclude that this error is reduced, if one is accustomed to watching the ordinary return of bile obtained by duodenal tube biliary drainage.

The present study is concerned then with the collection of duodenobiliary secretion by means of the duodenal tube in a series of patients chosen at random from those undergoing treatment in this department. The series comprises of 21 patients suffering from various types and degrees of gastrointestinal disturbances.

Procedure. A standard meal, consisting of one piece of buttered bread and one cup of tea, was given each patient 6 hours prior to intubation. Nothing by mouth was permitted thereafter. Duodenal intubation was accomplished and drainage was instituted until a constant flow of bile was obtained or the tip was definitely located in the duodenum by auscultation, whereupon 10 cc. of a 20 per cent solution of sodium dehydrocholate (Decholin-Sodium) were slowly administered intravenously. Thereafter for 90 minutes all fluid returning through the tube was collected in 9 test tubes—a tube for each 10 minutes of flow.

The control study was instituted on the same group of patients 1 week after the above procedure, utilizing the same meal with identical instructions and time limits. The duodenum was intubated, and after a constant flow of bile was obtained all the drainage was again collected for 10-minute periods, for a total of 90 minutes.

The following data concerning each of the 10-minute specimens collected were recorded: (1) Quantity of bile in cubic centimeters; (2) specific gravity; (3) color; (4) type of bile, whether A, B or C,* with reference to its origin in the biliary tract; (5) in addition, blood pressure determinations were made 20 minutes before administration of the sodium dehydrocholate and at 30-minute intervals thereafter; (6) the radial pulse rate was noted at the same intervals as the blood pressure determinations were made; (7) untoward effects were recorded as immediate, *i. e.*, during the intravenous administration, delayed, occurring during the time of the test, or remote, occurring during the week following the actual study.

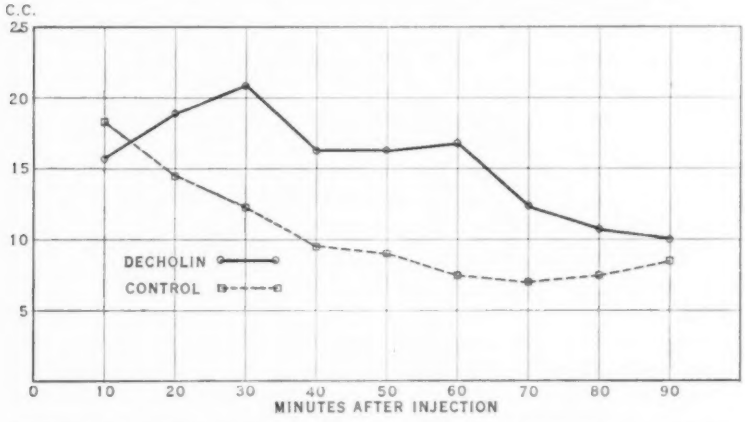

CHART I.—Composite graph of 21 patients showing the average amount of bile removed each 10 minutes over a period of 1½ hours, with and without decholin-sodium, administered intravenously.

Analysis of Results. 1. *Quantity of Bile.* (See Table 1 and Chart I.) The total quantity of return for the 21 patients over a 90-minute period after injecting Decholin was 2817 cc., or an average return of 134 cc. for each patient.

* "A" bile is arbitrarily designated as that derived chiefly from the extrahepatic ducts after Oddi's sphincter has relaxed.

"B" bile is designated as that derived chiefly from the gall bladder. It is darker yellow-brown than either "A" or "C" bile, due to the concentrating ability of the gall bladder.

"C" bile is designated as that derived chiefly from the liver, as freshly secreted bile. This bile is usually a light lemon-yellow color, offering a definite contrast to the darker yellow-brown, green or black "B" bile.

For further information consult: Non-surgical Drainage of the Gall Tract, by B. B. Vincent Lyon, published by Lea & Febiger, Philadelphia, 1923.

In the control experiment the return measured 1883 cc., an average of 80+ cc., or an average increase of 54 cc. after intravenous injection of sodium dehydrocholate.

Four patients showed less output of bile on the day of intravenous injection than on the control day. The amounts of these 4 cases were: following injection, 325 cc.; control, 421 cc.

Inasmuch as these figures were included in the total returns for the whole 21 cases who were tested, it is necessary to deduct these amounts if we wish to reach a conclusion concerning the bile flow response in the patients who reacted favorably to the injection. Thus 17 patients returned 2492 cc. following injection and on control testing returned 1462 cc. Average increase in these 17 cases was 60+ cc. The greatest individual increase was 120 cc. The greatest individual decrease was 46 cc.

The rate of flow is indicated in Table 1. The cholagogue effect of sodium dehydrocholate was most brisk at 20 and 30 minutes after injection, slightly less for the next 30 minutes, then becoming less during the final half hour.

TABLE 1.—AVERAGE QUANTITY OF DUODENAL RETURN IN 21 CASES FOLLOWING INTRAVENOUS INJECTION OF SODIUM DEHYDROCHOLATE COMPARED TO CONTROL STUDY WITHOUT SODIUM DEHYDROCHOLATE AT 10-MINUTE INTERVALS FOR 90 MINUTES.

Minute intervals.	Cubic centimeters after injection.	Cubic centimeters from controls.
10	15.6	18.2
20	19.0	14.4
30	20.5	12.1
40	16.1	9.5
50	16.0	9.0
60	16.5	6.5
70	12.4	5.9
80	10.75	7.4
90	10.2	8.0

2. *Specific Gravity.* It was not possible to arrive at an accurate conclusion relative to change of specific gravity. This was because: (1) The individual returns were in some instances too little to permit of estimation by even the smallest hydrometer; (2) the presence of the tip alone in some of the control tests seemed after 10 to 60 minutes to bring about a partial gall bladder response resulting in a delivery of various amounts of concentrated B bile having a higher specific gravity than the C bile. We were particularly interested in comparing the C bile obtained at each of the two examinations. Where these estimations could be made it was observed that postinjection specific gravities were slightly *higher* than those of the controls—an average of approximately 0.5 point. It was noted that only in 5 instances did B bile appear after injections of Decholin in 1 or 2 of the 10-minute specimens, whereas in the controls it was present in 13 instances, continuing more or less

constantly through the examination. Thus it might be inferred that this chemical has a slight inhibiting effect on gall bladder emptying.

3. *Color.* The same difficulty that we encountered in our specific gravity evaluation arose in our color comparisons. The presence of B bile interfered with making any accurate inferences as to color response other than that the controls were generally darker than the postinjection returns.

4. *Type of Bile.* This feature of our experiments has been discussed in the two foregoing sections. B bile appeared in only 5 of the patients after injection, whereas it appeared in 13 during the control test. Two patients showed B bile on both tests in from 1 to 4 of the 10-minute portions of the returns.

5. *Blood Pressure.* In 2 patients the blood pressure rose slightly within the hour after injection. In 1 patient the systolic pressure rose 5 points and the diastolic 10 points; in the second patient the systolic pressure rose 10 points and the diastolic 5 points.

Nine patients showed a fall. This occurred usually at the first 30-minute reading after the injection, less frequently at 60 minutes and rarely as late as 90 minutes. When the primary fall was found at 30 minutes there was no further reduction, but it was fairly well maintained throughout the test and showed only a slight tendency to return toward the normal. The greatest fall in the systolic pressure was 32 points and the least 5 points. The average for the 9 patients showing a reduction of blood pressure was 21 points.

The diastolic pressure fall ranged from 5 to 23 points; average, 10 points. One patient had a fall of systolic pressure of 10 points and a diastolic rise of 5 points. In another the systolic pressure fell 5 points while the diastolic rose 20 points.

All blood pressure in the control experiments remained relatively constant, *i. e.*, none showed any appreciable tendency to fall or rise. Of all the patients the highest blood pressure was 130 systolic and 80 diastolic and the lowest was 80 systolic and 50 diastolic. This latter patient caused us a little apprehension as we gave the injection, but his pressure remained unchanged throughout the test.

6. *Pulse Rate.* Four patients had a rise of pulse rate averaging 5 beats. Seven had a fall, averaging 5 beats. In the other 10 patients the pulse remained constant. The highest pulse rate recorded throughout all the examinations was that of 100 in a man before injection, which fell to 94 at 30 minutes and was back to his normal of 80 at 90 minutes. It was presumed that nervousness, due to the approaching vein puncture, caused this change of rate. The lowest pulse rate was 68 before injection and remained so throughout the test.

7. *Untoward Effects.* (*a*) *Immediate* (while giving injection). Only 1 patient complained of lancinating pain in the upper right quadrant during injection, transitory in nature. There was,

however, a common complaint of bitter taste occurring in from 3 to 10 seconds after the injection was begun. This symptom disappeared within 10 seconds after the injection was completed. Those who at some time or other had vomited bile stated that the taste was that of bile.

(*b*) *Delayed* (two hours succeeding injection). One patient caused us some concern 10 minutes after the injection was completed. He developed a rapidly increasing edema of the face, to the extent that in 20 minutes from the time it began he was unable to open his eyes. Respiration and deglutition were unaffected. The conjunctival vessels were markedly injected and there was profuse lacrymation. The skin of the whole body was suffused and hot. There was tremor of the voice and hands, and he stated that he "felt dreamy." At the 90-minute period he was again normal, except that he felt weak. This patient's blood pressure fell 25 points for both systolic and diastolic during the first 30 minutes, but was back to normal at 90 minutes. The pulse rate rose 8 points at 30 minutes. This patient has a bad myocardium, and at 50 years of age his arteriosclerosis was marked. He had had long-standing gall tract disease with probable hepatic cirrhosis. During the test he returned 100 cc. and while on control he returned 30 cc.

Ninety minutes after injection, on arising, another patient complained of nausea and prostration. This was followed by vomiting. Four hours later she had severe cramp-like abdominal pains with foul, greenish diarrhea—20 stools within 24 hours. Thereafter there was a rapid subsidence and quick return to normal. In her case the diagnosis was cholecystitis with cystic duct catarrh.

(*c*) *Remote* (after 2 hours). One patient suffering with cholecystitis developed abdominal pain 48 hours after injection, with nausea and profuse salivation, continuing 48 hours. Another complained of burning pain along the course of the colon for several weeks. This was considered due to a preëxisting mucous colitis. In no instance was there any tendency to venothrombosis, phlebitis or cellulitis following intravenous injection.

Conclusions. From the above facts determined by our study it is evident that sodium dehydrocholate in 2-gm. doses intravenously increases the fluid return through the tube from the duodenum. We believe that this increase of flow is due to the extra amount of thin liver bile, which seems to be excreted in response to the administration of this chemical substance. We inferred, however, that this substance seems to inhibit the gall bladder emptying function. No effort was made to determine the effect on cholesterol excretion from hepatic or duct epithelium.

In approximately 50 per cent of patients there was produced temporary hypotension. There was no appreciable change in pulse rate. There were no particularly untoward effects, either immediate or remote, except in the two instances cited. We, therefore, believe

sodium dehydrocholate can be considered a nontoxic bile salt that can be administered intravenously with reasonable safety. In this report its therapeutic usefulness was not investigated.

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A SURVEY OF DIPHTHERIA PREVENTION IN PHILADELPHIA.

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It is proper to consider immunity to diphtheria as a reason for failure to contract this malady. It is reasonable to assume that a highly immune population will have a lessened incidence and mortality from this disease. It is difficult to conceive of any survey that will give a mathematically accurate statement as to the actual immunity status in any large community. Practically every large city and many states have attempted to compile data that would show the progress made in establishing immunity to the disease by means of the administration of toxin-antitoxin or toxoid. Circuitous and complex methods have been employed by some agencies to obtain by cross section the immunity status of the nation. This has worked out to the satisfaction of some communities but has proved inaccurate in others.

Park and Zingher[1] established the proportion of naturally immune individuals that one might expect to find in given communities. These estimates have been verified by the author[2] and so many other observers in the past decade that they can be accepted without further reservation. That there has been no change in the natural

immunity status in the past 10 years is a matter of importance. It has not changed in the accepted childhood groups in Philadelphia. The almost universal decline in the incidence of diphtheria must be due, therefore, to some factor other than the natural immunologic status.

The early recognition of cases, their isolation, and the isolation of known carriers gave us an opportunity to estimate the value of these procedures and also showed us their fallacies long before active immunization against diphtheria was attempted. After a few years of experience with isolation one could hardly expect the precipitous decline in diphtheria incidence of the last few years. Case death rates have not declined to any great extent, consequently virulence has not materially changed. There has been no material or decided change in the percentage of diphtheria carriers recently in our communities, nor can the virulence of the organism be regarded as attenuated as a result of laboratory tests. The introduction of active immunization on a large scale has been followed by a precipitous decline in the incidence of diphtheria. It is necessary then to establish the relationship between active immunization and freedom from infection or to discover some other good and sufficient reason for diphtheria's decline.

A number of small towns, in a public-spirited fervor that one hopes will be a permanent feature of their community life, have immunized their children 100 per cent against diphtheria, with the result that no cases have occurred in their communities. In large cities any number of institutions have similar records, some of these institutions housing more children than the entire towns just mentioned. These observations would point the way to the necessity for wholesale active immunity in large communities.

Since the question has been raised that some communities have had a diphtheria decline with but a desultory effort at active immunization, it might be well to inquire into the facts concerning the accuracy of widely published statements to this effect. Some of these statements have been accredited to the highest authority and their statements are regarded as the acme of accuracy. For example, the White House Conference on Child Health has given estimates on the percentage of immunes in the infant and preschool group. Avidly accepted by the mass of medical and welfare groups interested in the study as accurate, they are not, at least in the instance of Philadelphia, anywhere near the demonstrable truth. Even as an indication of a trend, which was the real idea behind the compilation of these figures, they are disappointing since the student cannot find firm ground in them for the promulgation of logical thought. A real epidemiologic survey might reveal information that cannot be found at present concerning these communities. It is therefore pertinent that a large city give some statistical data regarding its work of immunization, its diphtheria case rate, and whatever might be of interest that would tend to establish a relationship between the two, or, on the other hand, contradict it.

Undoubtedly, the most important factor in the eradication of diphtheria would be the prevention of the disease in children below school age, since in this group occurs the largest number of cases. Table 1 shows the population of Philadelphia based upon the 1930 census.

TABLE 1.

Year.	Population.
1925	1,892,023
1926	1,904,431
1927	1,916,839
1928	1,929,247
1929	1,941,655
1930	1,954,063
1931	1,966,471

Table 2 gives the number of births occurring in the city of Philadelphia from 1925 to 1930.

TABLE 2.

Year.	Births.
1925	39,072
1926	38,646
1927	38,525
1928	36,903
1929	35,224
1930	35,548

This group shows that 225,918 children were born within the city limits and is therefore a reasonable estimate of our preschool age population. There should be deducted from this, however, 21,934 deaths, as indicated in Table 3, leaving a balance of 203,984 children, approximately 3000 or 4000 of whom really should not be included because of the fact that they are the offspring of people living outside the city limits who availed themselves of the facilities of Philadelphia hospitals.

TABLE 3.

Year.	Deaths from all causes in infants and children up to 6 years.
1925	4,308
1926	4,449
1927	3,379
1928	3,859
1929	2,952
1930	2,987

Immigration and emigration do not alter the actual number of children but are prone to reduce the number of immunes, so that the child population of Philadelphia of the preschool age group and under totals 200,984.

Every infant and child immunized by the Department of Public Health submits a signed written permission from its parents. On the reverse side of the permission blank space is provided for whatever treatment is given this particular child, together with the

date the treatment has been administered. This card is filled in at every visit by the physician performing the work. The cards of completed immunizations are filed in the main office of the Division of Child Hygiene. Incomplete or open cases are kept in the Center where the permission was originally given. Certificates of immunity are given to parents whose children have demonstrated that they have acquired immunity by reason of a negative Schick test performed 6 months or longer after the third injection of toxin-antitoxin. The following table shows the number of immunized children by years from 1926 to 1930.

TABLE 4.

Year.	Immunized children.
1926	8,861
1927	8,492
1928	26,990
1929	23,711
1930	28,198

This totals 96,252 children immunized by the Department of Public Health, of a group of 200,984 infants and preschool age children. This gives a percentage of 47.8 per cent of immunized children recorded in the Department files.

This percentage does not include children immunized by family physicians, hospitals not representing the Department of Public Health, and other independent welfare agencies. These sources have proved to be reluctant to supply accurate information concerning the extent of their work. This may be due to a failure to keep accurate records or a failure to realize the importance of accurate statistical data concentrated in a central point.

If we assumed that there were performed 5 completed immunizations by every physician in the city of Philadelphia in 5 years, discounting the welfare agencies and hospitals, a conservative estimate of approximately 12,000 additionally immunized children can be granted. It is conceded that a large proportion of physicians are specializing in the fields that do not come in contact with the preschool age child, so that the assumption that but one immunization per year per physician is a deliberately low estimate. This would bring the total of immunizations up to 53.8 per cent.

Hospital and welfare agencies could account for perhaps 1 per cent more, or in round figures a grand total of 55 per cent of the preschool age population is actively immunized against the disease. Of those children of preschool age receiving no immunization treatment, approximately 25 per cent are naturally immune, so that 66.25 per cent of the children of Philadelphia of the infant and preschool age group are immune to diphtheria.

The immunization of the school child has been carried on since 1925 and the following quotation from a communication written by Dr. Walter S. Cornell, Director of the Division of Medical Inspection of Public Schools, is illuminative:

"We know that of 97,810 children in the kindergartens and first three grades, 65,904 (67.4 per cent) were recorded as immunized, November, 1930. If we assume that the balance of the main group are 60 per cent immunized, we then arrive at a total figure of 143,292 pupils immunized out of the group of 226,795. This would be a proportion of 63.2 per cent.

"You may be interested in knowing the proportion of pupils immunized in our lower grades, as we have accurate information, and the disease diphtheria is most likely to exist in these lower groups. In November, 1930, we found 44 per cent immunized in the kindergartens, 61 per cent in grade one, 78 per cent in grade two, and 78 per cent in grade three. The figures increase with progress in the grades, because we repeatedly circularize the children until they are promoted out of the third grade, and thus each year we get a few children in the second and third grades who have heretofore refused to take the protective treatment."

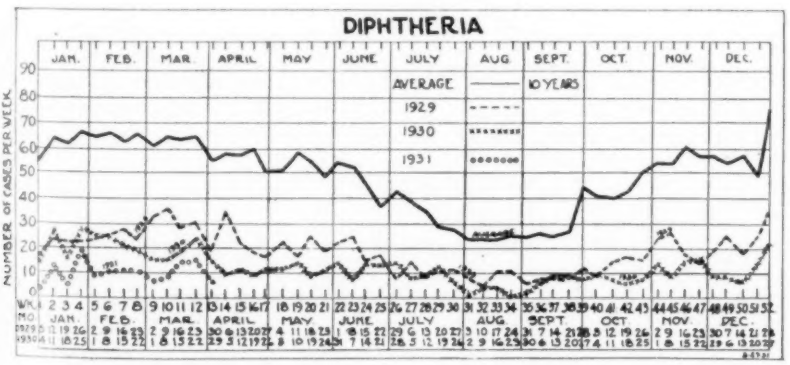
The incidence of diphtheria in Philadelphia will be noted as follows:

TABLE 5.

Year.	Case rate per 100,000 population.	Year.	Case rate per 100,000 population.
1919	207.9	1925	205.4
1920	184.0	1926	144.4
1921	183.6	1927	136.0
1922	165.5	1928	101.8
1923	177.3	1929	49.9
1924	206.1	1930	32.5

Table 6 is self-explanatory, as is also the chart:

CHART.



The number of cases of diphtheria occurring in the preschool age immunes in Philadelphia from 1925 to 1930, including the Department's children and those for whom immunity had been claimed but not proved, has been 40 cases. Of these, 21 cases occurred in

TABLE 6.—DIPHTHERIA FROM 1888 TO 1930, INCLUSIVE. Healthfax, November 25, 1929 **2**, No. 47.

Year.	No. of cases reported.	No. of deaths.	Case death rate.	Death rate per 100,000.	Year.	No. of cases reported.	No. of deaths.	Case death rate.	Death rate per 100,000.
1888	1,170	623	53.2	61.8	1910	3,804	492	12.9	29.08
1889	1,455	727	50.0	70.7	1911	3,792	498	13.1	30.37
1890	1,820	943	51.8	89.9	1912	3,080	388	12.6	22.85
1891	3,251	1,362	41.9	126.9	1913	2,626	359	13.7	20.59
1892	5,051	1,707	33.8	155.4	1914	2,610	329	12.6	19.97
1893	3,471	1,159	53.4	103.2	1915	2,613	317	12.1	18.71
1894	3,608	1,395	38.7	121.6	1916	2,499	390	15.6	22.7
1895	3,853	1,349	35.0	115.1	1917	3,141	441	14.0	25.64
1896	3,595	1,155	32.1	96.5	1918	2,477	384	15.5	21.9
1897	5,405	1,474	27.3	120.7	1919	3,763	445	11.8	24.15
1898	4,415	1,154	26.1	92.6	1920	3,368	413	12.2	22.74
1899	4,391	994	22.6	78.2	1921	3,382	318	9.4	17.36
1900	5,088	1,042	20.5	80.4	1922	3,069	281	9.2	14.83
1901	3,588	643	17.9	48.6	1923	3,310	270	8.1	14.04
1902	2,444	515	21.1	38.2	1924	3,874	275	7.1	14.09
1903	3,043	608	20.0	44.3	1925	3,887	315	8.1	16.1
1904	3,546	541	15.3	38.7	1926	2,750	266	9.6	13.55
1905	3,238	452	14.0	31.7	1927	2,607	220	8.4	10.81
1906	3,707	546	14.7	37.6	1928	1,964	230	11.2	11.1
1907	3,840	509	13.3	34.5	1929	969	89	9.18	4.25
1908	3,863	496	12.9	33.1	1930	635	48	7.55	2.46
1909	3,878	512	13.2	33.5					

The dispensing of antitoxin began in 1896.

the group of 96,252 children for whom the Department of Public Health claimed immunity.* Diphtheria in the preschool age group covering the period of this survey can be divided as follows:

	No. of cases.	Per cent.
Immunes	40	0.8
Nonimmunes	4872	99.2
Total	4912	

This extremely small number of cases among immunes would represent the human element of error in the interpretation of Schick reactions, and the number is insignificant as compared with the number of cases occurring from 1926 to 1930 inclusive.

The immunizations in the public schools were done on an intensive scale from 1925 to 1927 inclusive. The tables show a significant upward trend in the latter years, the preschool and infant age approaching the school immunization percentages. If the school-age child has been immunized beyond the recognized percentage proportions over the earlier age groups, then the number of cases should show a percentage increase in the least protected group.

Table 7, page 846, will show the cases arranged according to age and the percentage in each group.

At a glance it can be seen that the proportions, beyond reasonable fluctuation, have not changed, but the actual incidence has decreased.

One important factor must again be emphasized, that if active immunization is not effective in stamping out diphtheria, then the number of cases, whether the totals are decreased or not, should be proportionately divided between those so immunized and those not immunized, as expressed in their age groups. This is obviously not the case and the record of over 96,000 children must be considered.

Summary. Approximately 55 per cent of the children of infant and preschool age have been immunized against diphtheria in the city of Philadelphia, 47.8 per cent of whom have been immunized by the Department of Public Health; 66.25 per cent of the children of this age group and perhaps more of the school age group have either been immunized or are naturally immune to the disease. The incidence of diphtheria, since these figures have been attained, has been reduced 80 per cent. Ninety-nine and two-tenths per cent of the cases occurring in the city of Philadelphia occur in non-immunized children or in those in whom no immunity has been demonstrated. Less than 1 per cent of cases occurred in immunes.

* NOTE.—Covering the period of this survey 26 infants and preschool age children developed diphtheria in the Department's group of toxin-antitoxinized children before they had passed the period of immunity development: 24 were reported as being recently injected by private physicians. Since 11 per cent of our series require further immunization at the end of 6 months, these cases hardly indicate an increased primary phase (negative phase) susceptibility by reason of toxin-antitoxin administration.

TABLE 7.—DIPHTHERIA CASES ARRANGED IN AGE GROUPS AND PERCENTAGES OF THESE GROUPS ACCORDING TO ANNUAL OCCURRENCE.

Year.	1918.	1919.	1920.	1921.	1922.	1923.	1924.	1925.	1926.	1927.	1928.	1929.	1930.
Age—Under 1 Year.													
Cases	75	70	90	94	93	121	133	115	82	67	196	35	25
Per cent	3	2	3	3	3	4	3	3	3	3	10	4	4
Age—1 to 5 Years.													
Cases	1266	1561	1358	1302	1286	1278	1680	1685	1325	1379	945	528	330
Per cent	51	42	40	39	42	38	43	43	48	53	48	54	52
Age—6 to 10 Years.													
Cases	766	1560	1337	1368	1241	1220	1265	1395	881	717	488	248	145
Per cent	31	42	40	40	41	37	33	36	32	28	25	25	23
Age—11 to 15 Years.													
Cases	135	394	283	358	198	351	321	295	187	188	123	57	44
Per cent	5	10	8.4	10	6	11	8	8	7	7	6	6	7
Age—Over 15 Years.													
Cases	..	..	..	260	251	93	120	105	79	66	33	18	
Per cent	..	..	..	8	8	3	4	2	3	2	2	2	
Age—16 to 20 Years.													
Cases	66	73	72										
Per cent	3	2	2										
Age—Over 20 Years.													
Cases	..	..	..	..	..	247	355	292	196	190	179	42	52
Per cent	..	..	..	..	..	7	9	8	7	7	9	4	8
Age—21 to 30 Years.													
Cases	101	28	86										
Per cent	4	..	2.4										
Age—Over 30 Years.													
Cases	68	77	142	..	..	..	..	..	..	..	..	26	24
Per cent	3	2	4.2	..	..	..	..	..	..	..	..	3	4
Age—Over 40 Years.													
Cases	..	..	..	..	..	..	..	..	..	..	..	15	15
Per cent	..	..	..	..	..	..	..	..	..	..	..	2	2
Totals.													
Cases	2477	3763	3368	3382	3069	3310	3874	3887	2750	2607	1964	969	635

Bacteriologically, the disease is as virulent as ever, and the death rate carries on the even tenor of its way. No other new epidermiologic factor except active immunization with toxin-antitoxin has been utilized to combat the spread of infection and the older methods are as inadequate as ever. Destiny's finger seems to point definitely to active immunization as the weapon with which to combat and eradicate diphtheria.

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CLINICAL OBSERVATIONS ON THE SO-CALLED LEATHER-BOTTLE STOMACH.*

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Leather-bottle stomach is a term which has been attached to a number of conditions in which the stomach is contracted to that of a small organ of diminished capacity, and in which the walls are thickened rigid and present an entire loss of flexibility. Much confusion still exists regarding its actual significance, for although from a macroscopic viewpoint the general appearance of the stomach is the same, yet on close observation it presents various different lesions. Further confusion has arisen by the application of such terms synonomously as "linitis plastica," cirrhosis and sclerosis of the stomach as well as leather-bottle stomach.

The leather-bottle type of stomach was first described, by Andral[1] in 1834 and a condition recognized by Cruveilhier[2] in 1839, in which a special type of irregular hypertrophy of the stomach was present at and some distances beyond the pylorus with definite involvement of the submucosa. It remained, however, for Brinton[3] to name the

* Presented by title at the Meeting of the Association of American Physicians at Atlantic City, May 6, 1931.

disease "linitis plastica," and more fully to point out the pathologic changes occurring in the stomach in this affection, emphasizing especially its inflammatory state. Since then, the cancerous nature of this affection has been stressed by some and the chronic inflammatory by others, while it has been further suggested by Bensuade and Rivet,[4] as well as Lewald,[5] that it may even develop upon the basis of a syphilitic lesion of the stomach.

This lack of unanimity is largely due to the interpretation placed upon the pathologic processes. As has already been pointed out, a number of varied pathologic conditions may produce identical appearances in the gross specimens and unless careful microscopic investigations are undertaken, erroneous conclusions may be reached.

Wyard[6] has clearly presented this problem in a table, which we have taken the liberty of slightly modifying.

Leather-bottle stomach	1. Carcinoma	Diffuse and local	A. Sclerosing carcinoma or carcinoma plastica (improperly called linitis plastica).
			B. Other forms of carcinoma.
	2. Fibromatosis	Diffuse and local	

The difficulties encountered in differentiating these varied affections can be best recognized by a study of the individual pathologic processes.

Sclerosing Carcinoma, So-called "Linitis Plastica." This lesion may present one of two types, either localized surrounding the pylorus or a diffuse involvement of the entire organ. The second is the final stage of the local disease. A very rare form of carcinoma plastica has been described in which various other regions of the stomach have become involved in localized patches. As a result of the increase in connective tissue and thickening of the gastric wall, especially of the submucous layer, a diminution in size of the stomach is produced, leading to as small a capacity as 100 cc.

In the areas involved, the wall of the stomach is contracted and presents an entire loss of flexibility, is rigid and thickened and hard in consistency. The process takes its origin at the pylorus and progresses gradually toward the cardia in its involvement of the entire stomach. If the pylorus is alone involved, stenosis with dilatation of the stomach may be produced. The peritoneal coat presents a pearly white, dull appearance and not infrequently adhesions will be observed between the stomach and neighboring organs.

In its final stages, the stomach is sausage-shaped and greatly diminished in size, at times but 6.5 cm. to 7.5 cm. by 3.5 cm. and is thus converted into a rigid tube. The thickening ordinarily only involves the stomach itself and does not extend beyond into the duodenum, though a number of observations in which the intestines

FIG. 1.—Carcinoma plastica. (Courtesy of Dr. Allan J. Smith. From Rehfuss, Diseases of the Stomach, W. B. Saunders Company, publishers.)

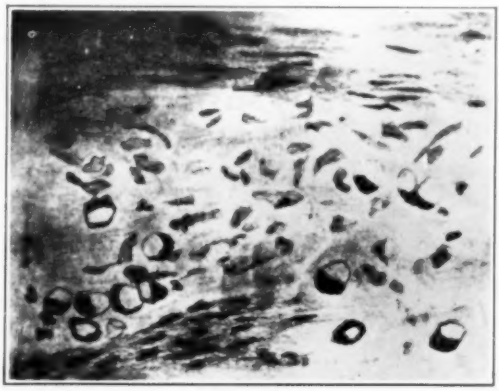

FIG. 2.—Section of stomach wall in region of pylorus showing signet-ring cells. (From Aaron and Wadsworth.)

FIG. 3.—Illustrates the roentgenogram of a case of leather-bottle stomach. Note the tubular, narrowed contracted stomach.

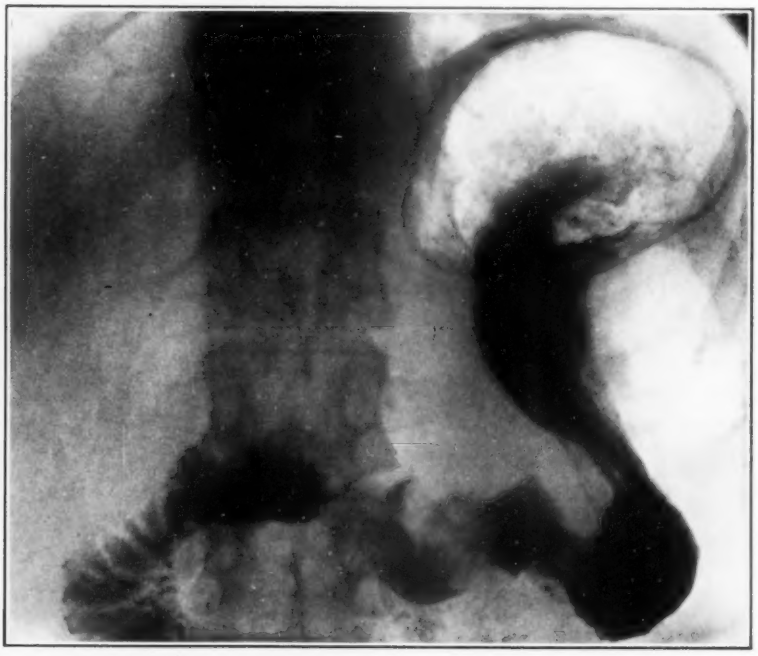

FIG. 4.—Shows another case of a markedly contracted stomach, diagnosed as leather-bottle stomach, and confirmed by operation.

FIG. 5.—Roentgenogram showing the tubular effect of the entire stomach, in a case of leather-bottle stomach. This represents the immediate view, and reveals the markedly rapid emptying of the stomach.

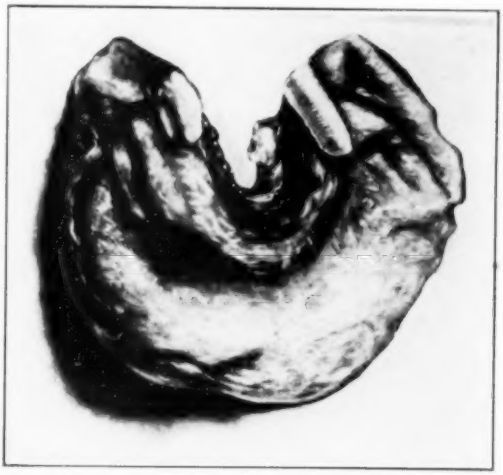

FIG. 6.—Leather-bottle stomach spread out showing partly opened lumen (fibromatosis type); autopsy specimen.

FIG. 7.—Roentgenogram of a small contracted stomach, which emptied with marked rapidity.

and other viscera were involved in a similar process have been recorded. Glandular involvement is not unusual. It was present in 15 of the 23 cases of Lyons.[7] According to Wyard[6] the glands may be hard, suggesting malignant infiltration, yet this is not always confirmed by microscopic examination. In a single instance of Baumgartner's, Cases' and Deegan's[8] 5 cases, cancerous involvement of the greater omentum was noted. On section, the various layers of the stomach may be recognized, though not nearly as definitely as under normal conditions. These are much thickened to the greatest degree at the pylorus and least at the cardia. The mucosa not infrequently presents a wrinkled appearance and is thrown into folds produced by the contraction of the other layers. The rugæ are often diminished in number and flattened and the mucosa itself may become entirely obliterated in certain areas. The greatest thickening is due to the increase of connective tissue in the submucous layer which may attain from 10 to 15 times its normal thickness, is white in appearance, and is hard and firm on section. This layer constitutes a large portion of the gastric wall. The muscular layer presents glistening fibrous bands with segmentation of the circular muscles by the fibrous tissue. The longitudinal muscles are only involved in the late stages of the disease. Interfibrillary infiltration of the muscle is absent to a great degree and there is but slight actual destruction or invasion of the muscular layer, connective tissue being present only between the muscular bundles.

Ulceration is not infrequent; it was present in but 5 (22 per cent) of the 23 cases of Lyons[7] which, however, is not in accord with the findings of Thomson and Graham[9] who observed it in 7 of 9 specimens (77 per cent).

On microscopic examination, the mucosa may present a normal appearance in certain areas with abundant secretion of its glands and increased discharge of mucus; in others degenerative changes in the cellular structure are noted, produced as the result of the interference with the blood supply by the contracting fibrous tissue. The submucosa is greatly thickened and represents at least a half of the increase in the gastric wall. Connective tissue fibers may be observed invading the muscular coat from the submucosa into the subserous and serous structures, interlocking one another and surrounded by numerous small bloodvessels. These fibers are not uncommonly nucleated. The muscularis is hypertrophied and interlaced with connective tissues extending from the submucosa. A thickening of the subserous coat due to the connective tissue increase is also noted.

In all of the coats of the stomach, but more especially in the submucosa in addition to the nucleated connective tissue cells already referred to, there are present numerous small cells containing irregular nuclei of varying size. These may occur singly or in groups and

resemble epithelial cells. Aaron and Wadsworth[10] give the following description of these cells: "Their cytoplasm is usually clear with no distinct membrane or is frequently represented by a large vacuole surrounded only by what appears to be a cell membrane. Within the vacuole a small globular mass staining deeply with eosin can be seen. These vacuolated elements usually have their nucleus pushed to the extreme periphery where it appears like a thickening of the membrane, giving the cell the form of a signet ring. These peculiar cells are found not only in the submucosa, but also in the connective tissue patches of the muscularis in the neighborhood of bloodvessels, where they often seem closely packed together.

"These elements have a decided degenerated character as is evidenced by their shapeless nuclei, structureless confluent chromatin and the vacuolization of their cytoplasm. From the staining reactions of the latter with hemotoxylin, it seems possible that the degenerative changes in the cytoplasm are of a mucoid nature. The nature of these cells cannot be definitely ascertained, yet they are strongly suggestive of epithelial cells found in certain forms of carcinoma of the stomach, especially the so-called Krukenberg carcinoma." (Figs. 1 and 2.)

The presence of pure mucin has been demonstrated by Reynier and Masson[11] in these epithelioid cells by means of specific stains. It is not clear according to Vecchi[12] whether these cells represent epithelial cells in mucoid degeneration or whether the cells secrete mucus and assume this peculiar tendency, due to the resistance produced by the connective tissue to the invasion of the cells.

According to Ewing[13] this type of carcinoma must distinctly be differentiated from the usual scirrhous cancer of the stomach in which with the diffuse thickening of the coats there is evidence of metastases as well as the presence of the usual carcinomatous cells. In carcinoma plastica there is on the other hand, a diffuse scanty infiltration of large cells with hyperchromatic nuclei and only slight tendency to metastasize. From a careful review of the literature, the evidence is becoming more and more convincing that "so-called linitis plastica," though formerly viewed in the light of a chronic inflammatory process, is now fairly well established as a carcinomatous process. It should therefore be dropped as a misleading term. While it may still be extremely difficult at times to interpret the epithelioid cells as carcinoma cells, yet evidence in this direction is constantly increasing. So eminent a pathologist as Ewing has definitely accepted this view, based on the fact that following a diligent study of his specimens, he has never failed to find the epithelioid cells with mucous degeneration and signet-ring nuclei as undoubted evidence of carcinoma. It is unquestionably true, that many of the earlier cases were studied imperfectly; for Curtis,[14] who in a report described a case as noncancerous, after a restudy of many sections was finally able to demonstrate cancer cells. How-

ever, the problem still remains complicated, since extremely careful histologic studies are always required to definitely establish the diagnosis. Nevertheless even in the absence of definite elements in the sections obtained it is not possible always to rule out malignancy nor does the absence of glandular metastases necessarily indicate malignancy of the so-called linitis plastica type.

Other Forms of Carcinoma of the Stomach. Aside from the cases of carcinoma plastica of the type already described, there are instances of carcinoma of the stomach from which these are clinically indistinguishable. These cases may present a local or diffuse involvement and may be according to Wyard[6] of the scirrhous, cylindrical cell or colloid type. Of these, the diffuse scirrhous variety is most common. This form of carcinoma is not usually difficult to distinguish from "carcinoma plastica" by the diffuse thickening noted equally in all of the coats of the stomach; the presence of unquestionable and easily distinguishable carcinoma cells as well as by metastases. The stomach in these cases is contracted and smaller than normal; the surface being roughened by the presence of numerous small nodules and the lumen is of diminished capacity. The mucous membrane is markedly involved and destroyed with the production of irregular indurated ulcerations. Wyard reports 3 instances of leather-bottle stomach due in one instance to a scirrhous, in another to a cylindrical cell and still another to colloid carcinoma.

Fibromatosis or Cirrhosis of the Stomach. There are undoubted instances of leather-bottle stomach of benign origin. They may occur in the local or diffuse form. Auneau,[15] Tassin[16] and Maier report cases of hypertrophic stenosis of the pylorus closely related to this condition. Henry and Osler[18] described a form of diffuse cirrhosis due to a chronic gastritis leading to atrophy of the stomach with features of pernicious anemia. Krompecker and Makai[19] recognize cases of the diffuse type attributed to chronic inflammation, the changes in the stomach being produced by fibrosis and muscular hypertrophy associated with edema. In Lyle's[20] most complete review of the literature of this subject, 68 cases of the benign variety of this condition are recorded. His own cases in which a gastroenterostomy was performed proved to be benign from the sections of the tissue removed and from the fact that the patient lived 11 years following the operative procedure. Bland-Sutton[21] considers the changes occurring in the stomach in this condition in the same light as that observed in the atrophic gall bladder in cholecystitis. As the result of an ulcer of chronic gastritis changes are produced leading to a cirrhosis of the stomach. In Wyard's[6] report, 2 instances of the local variety and one of the diffuse are noted, and Dwight[22] records two of the diffuse type.

Diffuse fibromatosis may have its origin as a local manifestation becoming progressive and finally may invade the entire stomach.

When the stomach is completely involved, it presents the typical picture of the leather-bottle stomach. The stomach at this stage is firm, greatly diminished in size and sausage-shaped. The lumen is narrowed and the pylorus usually contracted. The mucous membrane is largely replaced by the hypertrophied submucosa producing small nodular protrusions into the lumen. While the mucous membrane is largely destroyed, the submucous and muscular layers are much thickened by connective tissue growth and many of the muscular elements destroyed. At certain areas they are hypertrophied. The peritoneal coat becomes but slightly involved.

Microscopically, the walls of the stomach are found much thickened due to the increase of connective tissue; much of the mucosa has vanished, the remaining portion presenting a swollen appearance with edema. The glands are largely destroyed but in those areas in which they still persist, the epithelium is desquamated. The submucosa is largely replaced by connective tissue through which numerous fibroblasts and bloodvessels can be distinguished. These fibers extend irregularly in all directions. The muscular coat is also filled up with connective tissue which invades this area destroying many of the muscle fibers. Many of the latter show vacuolization with disappearance of their nuclei.

The following histories illustrate the various types of leather-bottle stomach:

Leather-bottle Stomach of the Carcinoma Plastica Type. **Case Reports.** Case 1.—E. K., a woman, aged 22 years, complained of vomiting with which she had been affected about 4 weeks and which continued daily together with acid eructations, pain in the abdomen and marked constipation. There had been considerable loss of weight. The patient was much emaciated. Nothing abnormal was detected on examination of the abdomen. The gastric contents revealed an achylia; total acidity, 10; free HCl, 0. A Roentgen ray examination of the gastrointestinal tract disclosed an extremely small vertical stomach with pyloric stenosis and marked retention. On account of the decreased size of the stomach with gastric retention the diagnosis of carcinoma plastica was considered. An operation was performed by Dr. McGlannan who found a very small contracted stomach with a narrow pylorus, which scarcely admitted the tip of the little finger. The wall of the stomach was 15 mm. in thickness, each layer showing distinctly, the muscular coat presenting the glistening fibrous bands. The mucous membrane itself appeared rather thin and the fibrous bands from the submucous layer showed up distinctly. A posterior gastroenterostomy was performed. Dr. McGlannan was definitely of the opinion that this case represented an instance of the carcinoma plastica type of the leather-bottle stomach though no pathologic study was available. The patient made a satisfactory recovery as the result of the operative procedure, gained in weight and strength for a period of nearly 4 years. She then began to lose flesh rapidly, gave indications of an extreme degree of anemia and died within 6 months. Since no pathologic examination was possible it is difficult to state definitely whether this case represents a carcinoma of the plastica type of leather-bottle stomach or the usual scirrhous form. The extremely small stomach, however, with the absence of metastases and the long duration of the disease rather tends to indicate that the type is probably one of carcinoma plastica.

Leather-bottle Stomach of the Scirrhous Carcinomatous Type. CASE 2.—W. H. K., female, aged 47 years, had complained for about a year of fullness in the stomach and regurgitation of food following meals. This condition had become greatly aggravated and was accompanied by excessive formation of gas and nausea but not with vomiting. The patient lost 82 pounds in weight during this period.

On physical examination the marked loss of flesh was evident. The abdomen was soft, extremely relaxed and a suspicious mass was palpable in the left upper quadrant of the abdomen, sausage-shaped and tender on pressure. The gastric analysis revealed an achylia; total acidity, 35; free HCl, 0. The Roentgen ray report of the stomach was as follows: Stomach is small, in normal position, tubular and sausage-shaped, cardiac orifice is irregular, and the motility is very rapid, the stomach being almost empty in 10 minutes. There is a distinct absence of peristaltic waves. Examination of the gall bladder by means of the oral administration of tetraiodophenolphthalein shows a large negative shadow.

The diagnosis of leather-bottle stomach of the carcinomatous type together with cholelithiasis was made. The patient continued to lose weight and strength, the digestive symptoms becoming more pronounced and she died after a few months as the result of a terminal pneumonia complicated by extensive malignant disease with metastases in the liver. (Fig. 3.)

The sudden appearance of the digestive symptoms in a patient of middle life with a rapid loss in weight and downward course and the presence of an epigastric mass associated with a nodular liver together with the finding of an achylia as well as Roentgen ray evidence seem to justify the conclusion that we are dealing with a carcinoma probably of a scirrhous type.

Leather-bottle Stomach of the Scirrhous Carcinomatous Type. CASE 3.—A. T., a man aged 46 years, had been subjected to digestive upsets, in the form of pressure, fullness, distention and constipation for years. There had never been any pain. During the last year the patient had frequently been nauseated but had not vomited until within the last few months. Since then, this symptom has become aggravated and is preceded by extreme nausea and epigastric pain. The patient has lost 25 pounds in weight during the past 3 months.

On physical examination, aside from the evident loss of flesh nothing of importance was revealed. The abdomen was soft, the liver was slightly enlarged and tender to pressure and the inguinal glands were somewhat enlarged. The gastric contents after an Ewald test meal showed a total achylia. A Roentgen ray examination disclosed a small left-sided stomach one-third the normal size. The diagnosis of leather-bottle stomach was made and operation advised. On opening the abdominal cavity, numerous hard nodular masses as large as a pea, and some even larger, were detected studding the peritoneum and omentum. The stomach was small, about one-third its normal size. A hard indurated mass enveloped the pylorus, extending as far up as the center of the greater curvature. The condition was definitely malignant and represented the carcinomatous form of leather-bottle stomach. The patient recovered from the effects of the operation but died 3 weeks later. (Fig. 4.)

The operative appearance of the lesion in this case together with the widespread metastases throughout the peritoneum and omentum strongly suggested the presence of a scirrhous carcinoma in this patient. Unfortunately no specimen was removed at the operation so that no sectional study was made to classify this case positively.

Leather-bottle Stomach of the Scirrhous Carcinomatous Type. CASE 4.—R. L. E. T., a female, aged 56 years, consulted us 6 weeks following the discovery by her family physician of a "serious trouble with her stomach"

during a complete examination for "neuritis." The patient presented no symptoms of gastrointestinal disease but due to the advice given her became rather alarmed and worried and lost about 15 pounds in weight. The only positive finding on physical examination was an indefinite sausage-shaped mass palpable mainly to the left of the umbilicus and below it. The lower pole of the right kidney was palpable but the liver was not enlarged and no tender areas could be detected. The laboratory tests, including the Wassermann reaction, blood chemistry and picture, revealed no abnormalities. A fractional gastric analysis disclosed a true achylia. The Roentgen ray examination showed a small fish-hook stomach with a slight deformity in the pyloric region suggesting an ulcerative lesion. The colon was prolapsed and there was an 18-hour retention present in the terminal ileum. The diagnosis of carcinoma of the stomach was made and an exploratory laparotomy urged. At operation a small stomach with a marked thickening of the pyloric third was found. A little more than the pyloric third of the stomach was removed and an end-to-end anastomosis was performed. On incising the resected portion of the organ no ulceration of the mucosa was noted, but there was considerable thickening of the submucous and muscular coats. On microscopic examination the sections showed a scirrhous carcinoma. The patient made an uneventful recovery. When last heard from 2½ years following operation, she was still in good health. This is an example of a leather-bottle stomach of the scirrhous carcinomatous type with a 2½ year's cure following resection.

Leather-bottle Stomach of the Scirrhous Carcinomatous Type. CASE 5.—G. C. F., a male, aged 24 years, complained during the past 5 months of loss of weight (50 pounds), difficulty in swallowing, fullness, and discomfort following meals and occasional nausea and vomiting. Up to the onset of his present trouble, he had always enjoyed good health. His physical examination aside from the evident emaciation revealed nothing of importance. The abdomen was generally quite sensitive to pressure but no definite masses and no enlargement could be detected. The laboratory tests were negative except for the presence of a true achylia gastrica. A Roentgen ray examination revealed a definite obstruction to both the liquid and breaded meal at the cardiac orifice of the stomach, there was also a narrowing in this region but no defects were noted. The stomach occupied a high position; it emptied rapidly due to a patency of the pylorus and showed a marked deformity over its entire length presenting an irregular tubular appearance suggesting a leather bottle stomach of the malignant type. An esophagoscopic examination disclosed a narrowing at the lower end of the esophagus but there was no evidence of malignancy.

At operation a leather-bottle stomach was found together with a general carcinomatosis involving the liver, mesenteric glands and peritoneum. A section of a resected gland revealed the presence of a scirrhous carcinoma. Following operation the patient rallied for a few weeks and was able to partake of a small amount of liquid nourishment but gradually weakened more and more, continued to lose weight and died 4 weeks later. (Fig. 5.)

Leather-bottle Stomach of the Fibromatosis Type. CASE 6.—I. P., a woman, aged 56 years, complained of indigestion at various times for a number of years; during the past 5 months her symptoms had become aggravated and there had been considerable nausea, vomiting, eructations, discomfort and pain at times following meals, together with a marked loss of appetite. She had lost 35 pounds in weight during the past few months. On examination the patient was found much emaciated, the abdomen was soft but no masses or tender areas could be detected. The gastric contents presented a total achylia with considerable amounts of lactic acid. A Roentgen ray examination could not be undertaken as the patient seemed too ill. A diagnosis of carcinoma was made notwithstanding the absence of a palpable mass.

At operation, the stomach was found extremely small, not larger than the size of a fist, nonadherent and the wall thick and rigid. The pylorus was much contracted. The patient was so badly shocked that further surgery had to be abandoned and the abdomen was closed. It was quite evident that we were dealing with a case of leather-bottle stomach. She died within 2 days as the result of shock. At autopsy, a very small stomach was found measuring 8 cm. by 4 cm. The stomach wall was much thickened, the mucous membrane was thin and denuded; the strings of white fibrous tissue appearing through the mucosa. The muscular layer revealed the glistening fibrous bands especially marked. The pylorus was so contracted that an ordinary probe could only be forced through with difficulty.

On microscopic examination the mucous membrane was found largely denuded, the submucous and muscular layers being much thickened by connective tissue growth and many of the muscular elements destroyed. The glands had disappeared to a marked degree but in those areas in which they still remained, the epithelium was desquamated. No evidences of malignancy could be detected. (Fig. 6.)

Leather-bottle Stomach of the Fibromatosis Type. CASE 7.—R. E. C., male, aged 41 years, consulted us for indigestion which first manifested itself 17 years previously. This consisted mainly of pain and distention following the ingestion of food. Sixteen years ago an appendectomy was performed without great relief. Upon a dietetic and medicinal regimen the patient managed to remain fairly comfortable for 5 years when similar symptoms of greater severity recurred. A diagnosis of duodenal ulceration with mucous colitis was then made and his symptoms were somewhat controlled with belladonna, alkalies together with frequent feedings. Recently, notwithstanding these measures, the distress has become markedly aggravated.

The examination now reveals an obese abdomen with a slight enlargement of the liver and an exquisitely tender area in the midepigastrium. The laboratory tests presented no abnormalities with the exception of the presence of a true achylia. The Roentgen ray investigation showed a retardation of the barium meal at the cardia but no definite obstruction was observed even following a breaded meal. The stomach appeared strikingly small, was of the cow-horn type, high position but showed no defects although the pylorus appeared somewhat narrowed. The peristaltic waves seemed obliterated and the meal flowed rapidly through a gaping pylorus. The duodenal cap could only be visualized with difficulty and appeared somewhat flattened and directed posteriorly up under the gall bladder region. The presence of a small irregular stomach with symptoms of long duration and subsequent course suggested a leather-bottle stomach of the fibromatosis type. (Fig. 7.)

Etiology. The etiology of the leather-bottle stomach of the carcinoma plastica, as well as of the scirrhous type, is necessarily unknown. On the other hand, such conditions as syphilis, alcoholism, cardiovascular disease, chronic gastritis have been considered as causative factors in the fibromatosis form.

Leather-bottle stomach occurs usually in adults. Of Lyle's[20] 126 cases, the largest number occurred between the 40th and 60th years. The average age of the 38 cases of Lyons[7] was 52 years. The disease is about twice as frequent in males as females.

It was observed in 3 males and 4 females in our series; the ages ranging from 22 to 56 years.

Symptomatology. The symptoms closely resemble those of carcinoma of the stomach. The onset may be abrupt or may be preceded by vague signs of indigestion. At first the symptoms are usually mild, consisting of anorexia, eructations and discomfort in the upper abdomen. These soon become more pronounced and are accompanied by fullness following small quantities of food, vomiting, abdominal pain, progressive loss of weight and strength as well as marked anemia. The pain is frequently of the ulcer type, that is, relieved by food and alkalies.

According to Carnot[23] when the pyloric sphincter is not involved in the process, it remains in a state of continuous contraction and inasmuch as the stomach can only hold but small quantities, food is ejected as rapidly as it is consumed, often presenting the picture observed in carcinoma at the cardia. If the pylorus, is however, involved it remains relaxed and the contents of the stomach pass rapidly through the orifice which continues unless stenosis is finally produced.

On physical examination an epigastric mass can usually be palpated which is hard but rarely tender. At times in advanced stages, the mass can be detected as a movable sausage-shaped tumor. A mass of this type was noted in but 2 of our 7 cases.

The gastric analysis usually reveals an achlorhydria. Of 30 of Lyons'[7] cases in which the gastric contents were examined, free hydrochloric acid was absent in 22 and but 8 had free hydrochloric acid ranging from 6° to 32°. Lactic acid has been noted in a few instances. A true achylia was present in all of our 7 cases.

Diagnosis. The Roentgen ray presents the best method of determining the presence of leather-bottle stomach. The stomach usually empties extremely rapidly in the diffuse form, appearing in the films as a narrowed tube with sharp outline. There is an entire absence of peristalsis. A filling defect is often observed involving a large area of the stomach. In the local form the pylorus is found narrowed and presents definite evidence of obstruction. There are no Roentgen ray signs differentiating carcinoma plastica from other forms of leather-bottle stomach; the picture is often not unlike that of other forms of cancer of the stomach. In fact, the diagnosis before operation is usually carcinoma; in one of Baumgartner's[8] cases it was ulcer. In Lyle's[20] report of 126 cases the diagnosis was only correctly made in 2 instances. The diagnosis of leather-bottle stomach should be considered in adults who present a sausage-shaped mass in the epigastrium, a true achylia, loss of flesh and the suggestive Roentgen ray signs referred to above.

Prognosis. The duration of life in leather-bottle stomach varies greatly according to the type of lesion. In the 33 cases reported by Lyons[7] the average duration was 23 months, the longest 15 years, the shortest 5 weeks. The average loss of weight was 21 pounds.

In Baumgartner's[8] series of 4 cases, duration of symptoms extended over a period of 1 year; in ours, from a few weeks to 17 years.

The symptoms of leather-bottle stomach are progressive, pyloric stenosis is common and unless surgical measures are instituted death occurs as the result of anemia, inanition, metastases and cachexia.

Treatment. This is definitely surgical. Until this procedure can be undertaken, the patient should be given small, frequent, easily digestible meals. If the pyloric obstruction is not too marked, duodenal feeding is indicated. In the light of our present knowledge of achylia gastrica in its relation to pernicious anemia, the question arises as to the value of liver feeding or ventriculin as a means of improving the general nutrition of the patient.

Sooner or later, unless operation is undertaken, the disease will prove fatal. Pylorectomy or gastrectomy are the operations to be recommended whenever possible. Occasionally, gastroenterostomy has been performed. Of Lyons'[7] 33 cases at The Mayo Clinic, in which 15 explorations, 3 gastroenterostomies and 15 resections were performed, there were 6 operative deaths. Of the 27 patients surviving operation 21 were dead.

Conclusions. From a study of our cases as well as those recorded in literature, the following conclusions may be drawn.

1. The term "leather-bottle stomach," as suggested by Wyard, should be reserved as a general term for a number of conditions which though similar in gross appearance, present, however, a varied pathology. Clinically, it is rarely possible to differentiate these types.

2. This condition may present a local or diffuse involvement.

3. The term "linitis plastica" should be discarded and a more appropriate term such as "carcinoma plastica" be substituted. This is represented by a small-cell epithelioid growth, having definite pathologic characteristics, the diagnosis of which cannot be made except following a most painstaking microscopic examination.

4. The clinical as well as Roentgen ray manifestations of leather-bottle stomach are similar, no matter what the characteristic pathologic changes may represent. These manifestations are largely those of carcinoma though there appears to be a type which is definitely not malignant.

5. The carcinoma plastica and fibromatosis forms produce death by inducing profound anemia and malnutrition; the scirrhous carcinomatous type largely as the result of metastases.

6. The treatment is surgical; the only hope for a complete cure lies in radical surgery, either in the form of pylorectomy or gastrectomy. Occasionally palliative measures as gastroenterostomy may afford relief.

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REVIEWS.

FRACTURES OF THE JAWS. By ROBERT H. IVY, M.D., D.D.S., F.A.C.S., Professor of Maxillo-facial Surgery, Graduate School of Medicine, and of Clinical Maxillo-facial Surgery, School of Dentistry, University of Pennsylvania, and LAWRENCE CURTIS, A.B. M.D., D.D.S., Assistant Professor of Maxillo-Facial Surgery, Graduate School of Medicine, and School of Dentistry, University of Pennsylvania. Pp. 180; 177 illustrations. Philadelphia: Lea & Febiger, 1931. Price, $4.50.

THE authors of this book are so well known from their previous publications and demonstrations on fractures of the jaws that their monograph may well be considered as authoritative on this subject. After thoroughly considering the anatomy of the parts and the symptoms and signs of fractures, a detailed discussion is given of the manner by which these fractures may best be handled.

The approved methods of treatment of fractures of the mandible are fully described. The treatment by wiring is discussed and excellent illustrations show how the lower jaw may be splinted against the upper teeth. The authors give their own methods of reducing displaced fractures by elastic (rubber band) traction attached either to the upper teeth or to a metal stay incorporated in a plaster head piece. Proper emphasis is placed upon mouth hygiene in the various methods of treatment.

The fractures of the maxilla and the zygoma are classified and appropriate treatment is described for each type. The chapter on Roentgenographic technique by Dr. Ennis clearly describes the approved methods of making Roentgen ray exposures for the individual types of fractures. Dr. Scogin gives an excellent chapter on the too-often-neglected dietary management of patients with fractures of the jaws.

The book is written so that he who runs may read. The text is profusely illustrated showing clearly the methods of treatment described in it. At the end of each chapter is a summary of the methods of treatment outlined according to the type of fracture. The monograph makes avilable to the general surgeon, the dentist and others who treat these fractures, the results of many years of experience in dealing with them. It is without doubt the most complete and useful book in its subject which has yet been printed.

L. F.

TEXT BOOK OF PHYSICAL THERAPY, VOL. I. By WILLIAM BENHAM SNOW. Pp. 708; 183 illustrations. New York: Scientific Authors' Publishing Company, 1931. Price, $10.00.

A SCHOLARLY presentation of a book on physical therapy giving outlines of method and dosage is a well-known want. The present book is divided into a section of 20 chapters on the Constant and Static Current and the diseases to be treated with it; another section of 14 chapters on the physics, physiology and therapeutics of High Frequency Currents and a final section of 8 chapters on Electrosurgery. While the book undoubtedly contains much valuable material, it attempts so much not strictly in its domain that more pertinent material is often inadequately treated. It also seems as if too widespread claims were made for treatment of various conditions that are usually considered to be better handled in other ways.

E. K.

HEALTH ON THE FARM AND IN THE VILLAGE. By C.-E. A. WINSLOW, DR. P.H., Professor of Public Health, Yale School of Medicine. Pp. 281; illustrated. New York: The Macmillan Company, 1931. Price, $1.00.

THIS book is a review and an evaluation of a county health demonstration carried on with the coöperation of the Milbank Memorial Fund in Cattaraugus County, New York from 1923-1929. In addition the author considers the applicability of a similar complete public health program to other rural areas. The outstanding lesson, according to Dr. Winslow, is the "urgent importance, the great difficulty and the high cost of adequate health service for rural communities" (p. 16). To carry on such a program under reasonably comparable conditions would cost about $2.50 per capita.

The detailed tables and the keen analysis probably make this statement the most thorough study not only of the experience in one county but of the problems involved in securing necessary health supervision for the rural population of the United States.

A. F.

NOGUCHI. By GUS ECKSTEIN. Pp. 419; illustrated. New York: Harper & Bros., 1931. Price, $5.00.

UNQUESTIONABLY one of the most picturesque figures among medical investigators of this century, Noguchi explored realms still too little mastered to permit any worth-while attempt at evaluation today. Perhaps this is the justification for the colorful way in which his present biographer has chosen to envisage his subject. Approach-

ing perilously near the prevalent fictional type of biography, which is bad at best but most pernicious if applied to scientists, the author has chosen to dramatize in jazzy style the man and the eccentricities of his startling career.

Born a peasant farmer's son in 1876, at the age of 3 Seisaku (who later changed his name to Hideyo on reading of a character named Seisaku who came to a bad end) so badly burned hands and feet that one hand remained permanently mutilated, though they were far from the stumps that the author alludes to (p. 53). The worst hand was later "reconstructed" by an enlightened provincial doctor—whence his stimulus to study medicine—and was an efficient aid to its owner's marvellous technical skill, as I can personally testify. Noguchi's financial difficulties in completing his medical studies, his ability to squander borrowed money, his chance encounter with Dr. Simon Flexner at Kitasato's Institute, which was later to bring him to Philadelphia first as assistant then as Demonstrator in Pathology at the University of Pennsylvania and to start him on Snake Venoms with Weir Mitchell, all are entertainingly and apparently accurately told. While Noguchi was in error in writing that "there is a rule not to employ foreigners" at the University, funds were scarce but were eventually procured through Dr. Mitchell. Within a year the Rockefeller Institute was organized with Flexner as its head, so Noguchi was sent on a Carnegie Fellowship to Madsen's Serum Institute at Copenhagen, before taking up his work at the new Institute which was to continue until his tragic death "in line of duty" in West Africa in 1928.

Noguchi's work on venoms stands firm and with his fertility in developing technical methods is sufficient to rank him one of the most influential bacteriologists of his day. Even though his work on trachoma and rabies, the globoid bodies of poliomyelitis, the cultivation of the Spirocheta pallida, and the spirochete that he thought was the cause of yellow fever still must await evaluation, his accepted contributions are more than sufficient to assure him lasting fame.

Of the man himself, Eckstein has given an inclusive, forcible and colorful picture. His tremendous energy when aroused, alternating with periods of "incredible laziness," his oriental artistry, his absorbing passion for research, his vivid love of life receive sympathetic and efficient handling by a friend who has given loving care to his work.

Noguchi's imaginative fancy runs through many passages quoted from his correspondence: "At that time I will be in the springtime of 27 or 28, with blood and spirit in vigor, and that is not too late to shake my arms around and to feel heaven and earth too small." . . . "I cannot speak yet concerning my final purposes and desires, but once I go abroad and succeed, I will speak again. If I speak before, it is forcing the bud unwillingly and there is no per-

fume, nothing. Therefore silence is the flower. Please be sure to cover this from those not concerned." "If it falls before it blooms what is the plum blossom?" "At my parting you showed me kindness like sea and mountain. . . . Colds are source of every disease, so I hope the master will take care of honorable wife. . . . Please remember me to all who have eaten out of the same kettle. With bent neck."

His reply to a request for biographical details is also illuminating. "Born, practiced dentistry, studied medicine, taught physiology, learned not much; read two or three men, learned a little; came to know two or three women, learned a good deal; made friends with two rats, learned prodigiously; wrote about the rats, continued to write." E. K.

AN INTRODUCTION TO GYNECOLOGY. By C. JEFF MILLER, M.D. Professor of Gynecology, Tulane University School of Medicine. Pp. 327; 117 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, $5.00.

As the title indicates, this book is merely supposed to be for the student who is beginning his course in gynecology and was written because the author was convinced that such students lack the ability to use the more extensive works selectively. Therapy is not discussed because the author believes that the treatment of disease is no concern of the junior student. The book well fills the gap between a simple outline and the usual textbook and is replete with present-day views on gynecology, especially in the sections devoted to physiology and internal secretions. The illustrations, although practically all taken from other standard books on the subject, are adequate for a treatise of this size except in the section on the development of the female genital organs. This subject, which is usually quite confusing to students, could be better elucidated by one or two carefully selected diagrammatic sketches. His students, for whom the book was compiled, can be thankful to him for the efficient manner in which he has selected the latest thoughts of the foremost gynecologists and incorporated them in such a small book. F. B.

RECENT ADVANCES IN PULMONARY TUBERCULOSIS. By L. S. T. BURRELL, M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), Senior Physician to Royal Free Hospital. Pp. 240; 49 illustrations. Second Edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1931. Price, $3.50.

IN the preface to the first edition of this book the author says "Most of the book deals with treatment, and no attempt has been

made to describe physical signs or morbid anatomy, because the work is intended for practitioners and senior students and not as an examination textbook." In the preface to the second edition he says "The book is intended to bring to the notice of the practitioner and senior student the recent advances in our knowledge of tuberculosis and is not a treatise for the specialist."

With these limitations the book hardly lives up to its title for about two-thirds of the space is devoted to treatment, the other third being given to a mere statement of certain fundamental and well proven facts about tuberculosis in general. Also the word "Recent" must not be taken too literally as the new treatments discussed were first proposed 10 to 20 years ago, but after all this is in keeping with the general tempo of a disease the treatment of which is measured in years.

Pneumothorax is treated at some length but the other methods of treatment referred to are given only two or three pages at most. The most recent advance in the surgical treatment of pulmonary tuberculosis, namely phrenicectomy and thoracoplasty, are only referred to very briefly. In all this the author voices his own experience and quotes from his own cases to an extent that makes it impossible to consider this a broad cross section of general opinion on the subjects discussed. R. E.

BOOKS RECEIVED.

NEW BOOKS.

A System of Bacteriology in Relation to Medicine. Vol. 9. Technical Methods—General Index. By various authors. Pp. 363; 86 illustrations. London: Medical Research Council, 1931. Price, £ 1.1.9 for this volume; for the set £ 8.14.9. Obtainable in the United States at British Library of Information, 5 E. 45th St., New York City.

The Surgical Clinics of North America, Vol. 11, No. 5 (Pacific Coast Surgical Association Number, October, 1931). Pp. 279; 109 illustrations. Philadelphia: W. B. Saunders Company, 1931.

Tables of Food Values. By ALICE V. BRADLEY, B.S., Supervisor and Instructor of Nutrition and Health Education, State Teachers College, Santa Barbara, Calif. Peoria, Illinois: The Manual Arts Press, 1931. Price, $2.00.

Simplified Diabetic Management. By JOSEPH T. BEARDWOOD, JR., A.B., M.D., F.A.C.P., Chief of Diabetic Clinic and Associate Visiting Physician, Presbyterian Hospital in Philadelphia, and HERBERT T. KELLY, M.D., A.A.C.P., Associate in Diabetic Clinic, Presbyterian Hospital in Philadelphia. Pp. 191; 7 illustrations. Philadelphia: J. B. Lippincott Company, 1931. Price, $1.50.

Lezioni di Medicina Biologica. By C. MARTELLI. Pp. 548; illustrated. Naples: Edizioni Rinascenza Medica, 1930.

The Early History of Yellow Fever. By HENRY ROSE CARTER, M.D., Assistant Surgeon-General (Retired) United States Public Health Service. Edited by LAURA ARMISTEAD CARTER and WADE HAMPTON FROST. Pp. 308; 5 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, $5.00.

Physicians' Manual of Birth Control. By ANTOINETTE F. KONIKOW, M.D. Pp. 245; illustrated. New York: Buchholz Publishing Company, 1931. Price, $4.00.

The Child from One to Six. His Care and Training. Publication No. 30. Pp. 150; illustrated. Washington: U. S. Department of Labor Children's Bureau, 1931.

A useful, practical guide that should have w[illegible]ribution in American homes.

Pathology, Bacteriology and Applied Imm[illegible]gy for Nurses. By ROBERT A. KILDUFFE, A.B., A.M., M.D., F.[illegible].C.P., Director Laboratories, Atlantic City Hospital. Pp. 324; 112 illustrations. Milwaukee: The Bruce Publishing Company, 1931. Price, $2.50.

A Text-book of Neuro-anatomy. By ALBERT KUNTZ, PH.D., M.D., Professor of Micro-anatomy in St. Louis University School of Medicine. Pp. 359; 197 illustrations. Philadelphia: Lea & Febiger, 1931. Price, $5.50.

Medical Films and Their Sources. By WILLIAM F. KRUSE. Chicago: Bell & Howell Company, 1931. Gratis.

A survey of 538 reels of 16-mm. films on medico-surgical subjects with information as to how they may be obtained.

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PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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AND
JOHN H. MUSSER, M.D.,
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Infection in the Epidemiology of Undulant Fever in the General Population and in Selected Groups in Iowa.—It has been observed that occasionally in individuals in whom there is no evidence of undulant fever there will be found positive agglutination reactions, although in the majority of instances there is a close relation between the clinical evidence of the disease and the positive agglutination. In borderline cases, however, it should be necessary to know, in order properly to interpret the results, the incidence of infection in the general population. JORDAN (*J. Infec. Dis.*, 1931, **48**, 526) studied the results of agglutination tests on specimens of blood serum giving negative Wassermann reactions which would represent the general population. The sera of a group of people who had come in close contact with presumably infected cattle were also tested. These persons represented veterinarians, healthy employees of packing houses and a selected group who used raw contaminated milk. This latter group was selected because of the fact that it is very generally assumed that Brucella infection is transmitted through either direct contact with livestock or through the consumption of raw dairy products. In the present study there were used 1026 sera sent to the state laboratory for Wassermann tests. In this series there was no agglutination in approximately three-fourths of instances, but in about 25 per cent there was partial or complete agglutination in lower dilutions, while 0.3 per cent showed agglutination at 1 to 40 and 1 to 80. A questionnaire was sent to the physicians who sent these sera in asking for information regarding the people who showed partial or complete agglutination. One hundred seventy-six of these were answered. The great majority of these individuals had no contact with livestock, but it was found that contagious abortion of cattle was prevalent in 25 per cent of the cows in that community

and in 14 per cent infection was present in hogs. In only 3 instances was a past history given of an afebrile attack which might have been undulant fever. From these studies it is deduced that since nearly 8 per cent of the general population has no contact with livestock, presumably the use of raw dairy products accounts for their agglutinations for Brucella. A group of veterinarians was studied. One hundred and twenty sera were examined, 66 of which were negative and 54, or 45 per cent, showed partial or complete agglutination in dilutions of 1 to 5 to 1 to 40, 5 per cent showing partial or complete agglutination in the last dilution. As the veterinarians definitely showed a higher agglutination ratio than the general population, it was assumed that this is due to the greater contact with cattle. With the workers in packing houses the figures were even more striking. Of 220 sera 152 were negative, whereas the remainder showed a relatively high agglutination titer, 14 per cent showed a complete agglutination in 1 to 80 to 1 to 1280. In this group 14 gave a definitely suggested history of undulant fever. In a group of individuals that were using a milk supply that was known to be contaminated, 70 per cent showed no agglutination and the remainder partial or complete agglutination in titers from 1 to 5 to 1 to 640. Infection with Brucella melitensis under any circumstance seems to depend upon the amount of raw dairy products consumed, the ratio of exposure and the number of organisms ingested. In addition to the deductions already drawn, Jordan raises the question as to whether or not natural immunity may not be a factor, particularly in children, which might explain a large number of reactions which showed "no agglutination."

SURGERY

UNDER THE CHARGE OF
T. TURNER THOMAS, M.D.,
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Tumors of the Extrahepatic Bile Ducts.—SHAPIRO and LEFVENDAHL (*Ann. Surg.*, 1931, **94**, 61) say that a clinical and pathologic study is presented of 15 cases of tumor of the extrahepatic bile ducts. These included 1 amputation neuroma of the cystic duct, 1 solid adenoma, 1 congenital cyst and 12 carcinomas. According to this material carcinoma of the extrahepatic bile ducts was twice as frequent as carcinoma of the gall bladder and three times as common as carcinoma of the head of the pancreas. It should be given, therefore, greater consideration in the differential diagnosis of lesions of the porta hepatis. The clinical course, especially that part of it which was severe enough to demand medical treatment was brief. The clinical syndrome was usually a typical jaundice and was usually not the first symptom. It was usually not painless and it was not always steadily progressive. The clinical picture was often masked by symptoms arising from accidental complications, particularly duodenal ulcerations or from metastases. The tendency of these tumors to colloid degeneration with

numerous goblet cells is an expression of the original intestinal character of the bile-duct epithelium. The frequency of duodenal complications is noteworthy. Metastases were common, extensive and widespread and in some cases dominated the clinical and pathologic picture. Small as they are, contrary to current conception, these tumors send out metastases long before they announce their own presence. This may account for the present ungratifying permanent results of radical resection.

The Treatment of Lung Abscess and Empyema by Packing.—Connors (*Ann. Surg.*, 1931, **94**, 38) state that the pleural cavity is cleaned within 24 hours and remains grossly clean until the cure is effected. By the old method change of dressings daily or twice daily was necessary or else extensive apparatuses were employed. Even with the simple procedures close attention to details was necessary. By this method dressings are changed at comparatively infrequent intervals and may be forgotten for several days. The introduction of tubes is unnecessary and therefore a source of pleural irritation is removed. It is well known that drainage will continue as long as a tube is allowed to remain in a sinus. It is also noteworthy that no cases of osteomyelitis of the rib developed in the cases since there was no tube to rub for days against a rib adjacent to a thoracotomy wound. It prevents the discomfort which may be due to a mobile mediastinum by fixing it. In several cases when the tight packing was removed discomfort was experienced which was relieved by the reinsertion of the packing. The large thoracotomy wound with the help of the Cameron light permits of a perfect inspection of the pleural cavity and allows the operator to remove all fibrin and break up the necessary adhesions and pockets. And not least interesting it has allowed a clear view of the mechanism of the cure of the empyema cavity and has helped improve the methods directed toward cure.

Collateral Respiration in the Lung.—Allen and Lindskog (*Surg., Gynec. and Obst.*, 1931, **53**, 16) declare that the branches of the bronchial tree in a single lobe of the lung intercommunicate at the periphery in such a manner as to permit the transfer from one to another of gases, fluids and particulate matter. The process of transfer is referable both to diffusion and to passage through minute openings, but this point requires further investigation. The airways of two neighboring lobes do not so communicate. This bears economic significance to respiratory function after bronchial obstruction; for a lobule of lung with centrally obstructed bronchus may yet breathe satisfactorily by using the peripheral interconnections with adjacent free lobules. This function is termed collateral respiration. Collateral respiration plays two economic rôles in the lobular form of bronchial obstruction, namely, that of preventing the development of atelectasis and that of rendering important assistance to the bronchoeliminative forces. Collateral respiration may be excluded by closure of those airways along the margins of the obstructed lobule, which have to do with the intercommunication. This may result from blockage with secretions or

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other materials or from shutdown during periods of shallow breathing. The latter circumstance is probably a factor in the pathogenesis of postoperative atelectasis.

Carcinoma of the Breast in the Young.—Lee (*Arch. Surg.*, 1931, **23**, 85) claims that cancer of the breast in young women is a much more menacing disease than it is in mid-life or in old age. The course is often dramatic in its rapidity, almost simulating an infectious process. When the first symptom is a diffuse enlargement of the breast, a redness overlying the mammary gland or pain, surgical intervention is futile. A more careful examination of younger as compared to older women must be exercised before radical operation is undertaken. Early recurrence is more frequent in younger than in older women and indicates either a poorly chosen case for surgical intervention or poor surgical technique or both. In many of these patients reliance must be placed entirely on radiation therapy. In well-chosen cases well-planned adequate irradiation combined with carefully performed radical amputation yields the best results.

THERAPEUTICS

UNDER THE CHARGE OF
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For and Against the Nirvanol Treatment of Chorea Minor. Goebel (*Deutsch. Med. Wchnschr.*, 1931, **57**, 1313) presents a clear discussion of the advantages and disadvantages connected with the treatment of chorea minor by nirvanol (phenylaethylhydantoin). He points out from his own experience and that of a number of others that the appropriate administration of this drug yields better results in the treatment of chorea than are given by any other means yet employed. Its administration not only controls the symptoms of chorea but there is strong evidence to show that it greatly diminishes the frequency of the development of endocarditis. The most satisfactory plan of treatment is the administration of large daily doses of nirvanol, which are to be continued up to the beginning of so-called nirvanol sickness but in no event for longer than 12 days. Against the striking therapeutic value of nurvanol are, however, a number of serious objections. Among these there is the fact that the drug must be pushed to the point of developing moderately severe intoxication manifested by skin eruption, high temperature and a pronounced leukopenia. In the majority of cases cessation of administration is followed within a comparatively few days by subsidence of these manifestations, but in some they are certain to progress and in others, after subsidence of the symptoms, their recurrence may take place spontaneously. There is conclusive

evidence that the leukopenia is due to a definite depression of bone-marrow function. Along with the other symptoms mentioned there are also anginal manifestations in the throat, stupor, muscular cramps, cyanosis and frequently inflammation of the submaxillary glands. Definite instances of nephritis are furthermore encountered as a result of the actions of nirvanol and in several instances these have lead to death of the patient. The author concludes that, although nirvanol has proved to be a most valuable therapeutic agent in chorea minor, its administration is associated with such severe manifestations of discomfort and even with such risks of serious or fatal intoxication that its use cannot be recommended except in severe cases and then only after all other remedies have failed.

The Effect of Roentgen Rays in the Treatment of Bronchial Asthma, Eczema and Hay Fever.—The reports of the effect of Roentgen rays on certain allergic conditions is based mainly on animal experiments and scattered case reports. SCHREW and WILLMS (*München. Med. Wchnschr.*, 1931, **20**, 832) confirm, on the basis of their observations on patients, the beneficial effect of Roentgen rays on bronchial asthma, eczema and hay fever. Of the 9 cases with hay fever treated 6 were "cured," 1 improved and 2 remained unchanged. The authors claim that the therapeutic effects were not due to psychic influence. The nose and the mediastinum were the areas exposed to Roentgen rays in these patients. Of the 14 cases with bronchial asthma receiving treatment over the mediastinum, 8 were cured, 4 showed improvement, and 2 remained unchanged. Of 14 cases with eczema and evidence of cutaneous hypersensitivity following Roentgen ray treatment, 9 showed a diminished cutaneous reaction, in 4 the reaction was unaltered and in 1 it was more intense. The authors claim that in these conditions the Roentgen rays produce a desensitization.

PEDIATRICS

UNDER THE CHARGE OF

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OF PHILADELPHIA.

Pertussis.—MAGEE (*J. Am. Med. Assn.*, 1931, **97**, 922) feels that rectal ether is the treatment of choice for pertussis in view of the consistently good results obtained with it and the ease of its administration. When ether was used alone or in conjunction with other methods such as vaccines and ephedrin it gave rise to a greater reduction in leukocytes per day than the other commonly used methods. As a preventive measure, rectal ether was of no value in 10 cases in which it was used for prophylaxis. The constant bathing of the respiratory mucous membrane with a weak solution of ether probably accounts for its favorable results. Rectal ether greatly ameliorates the severity of pertussis and shortens its course, especially when begun in the paroxysmal stage. Its influence is greater among children over 1 year of age.

White and differential blood counts and isolation of the Bordet-Gengou bacillus give two reliable aids in arriving at an early diagnosis of pertussis. The latter method furnishes a means of enforcing a scientific quarantine and is a means of reducing the incidence of the disease. While rectal ether is not considered a specific for pertussis and while it may add little to the armamentarium for that disease, its simplicity and its effectiveness from the standpoint of symptomatic relief justify its use until a better form of treatment is found and proved superior.

Cod-liver Oil Emulsified in an Extract of Germinating Grains: Its Tolerance by the Infant Gastrointestinal Tract and Its Prophylactic Value.—Jarvis (*Arch. Ped.*, 1931, **48**, 502) found that deficiency disease prophylaxis became more efficient when vitamin sources are combined in a mixture of such tolerance to the infant's gastrointestinal tract as to permit its early and continued routine use during the early months of life, during which time hesitancy is usually encountered in undertaking such a procedure with the more common diversified sources of such administration. An emulsion of cod-liver oil in a concentrated extract of the germinating grains of wheat, oats and malted barley was found to be exceptionally well tolerated by the infant's gastrointestinal tract. This emulsion contained vitamins A, B and D but lacks vitamin C, which should be added by adequate doses of orange and tomato juice. Although containing 30 per cent by volume of cod-liver oil, this mixture yields a vitamin D potency equal to that of the pure cod-liver oil. This is probably due to the greater availability in assimilation due to the complete emulsification by the gastrointestinal tract and also possibly due to a coördinating activity of the A and the B factors.

The Early Diagnosis of Rheumatic Heart Disease in Children.—Seham, Shapiro, and Hilbert (*Am. J. Dis. Child.*, 1931, **42**, 503) states that in 809 patients admitted during a period of 7 years, 46 per cent of the cases were diagnosed as organic heart disease and 54 per cent as "no heart disease." Of 379 cases of organic heart disease, 18 per cent were congenital lesions of the heart, 74 per cent were rheumatic in origin, 3.6 per cent were due to other causes and 4.4 per cent were undiagnosed. For early diagnosis of heart disease of rheumatic origin all available methods were necessary. The problem of differential diagnosis revolves around chiefly the children who present the following symptoms: systolic murmur, with or without circulatory signs or symptoms; rheumatism and a systolic murmur that has escaped carditis; rheumatism and a systolic murmur that ultimately develops into chronic endocarditis; and congenital heart disease, especially patency. According to the statistics of this study, the most reliable means of diagnosis was history. A questionnaire was found to be more effective than informal questioning. Rheumatism alone caused 39.3 per cent of rheumatic heart disease. Rheumatism in combination with other causes was responsible for 83.1 per cent. Growing pains alone accounted for 2.3 per cent. The roentgenogram taken at a distance of 6 feet was found to be as reliable method for the practical purpose of diagnosis as the orthodiagram. The 50 per cent cardiothoracic index that is used as normal standard was found to be statistically not reliable. In 66 per

cent of normal children the cardiothoracic index is between 44 and 50 per cent, and the remaining 33 per cent fall between 41 and 51 per cent. In 25 of 100 consecutive examinations of normal children, one is likely to find a cardiothoracic index of over 50 per cent. A positive esophogram reveals a dilatation of the left auricle. This does not appear in children with congenital heart disease, in those with miscellaneous heart disease or in normal children. The esophographic results were positive in 55 per cent in cases diagnosed as mitral regurgitation. In this group the esophogram is more sensitive than auscultation. It gives positive observation in 67 per cent in the group diagnosed as double mitral disease and 77 per cent in those double mitral disease and aortic regurgitation. The so-called functional tests are of no value in determining the myocardial sufficiency of the heart.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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An Appraisal of the Newest Arsphenamin Synthetic, Bismarsen, in the Treatment for Syphilis, Based on 7666 Injections in 341 Cases During 5 Years.—STOKES, MILLER and BEERMAN (*Arch. Dermat. and Syph.*, 1931, **23**, 624) summarize a 5-year study of bismarsen. Some of their most important conclusions are as follows: (1) Local reaction to intramuscular injection (the only route) occurs following 2 per cent of injections as stiffness and moderate pain, most marked on the second or third day. It is largely controllable by prolonged massage, good technique and hot applications. (2) Systemic reactions occur following 0.5 per cent of injections, or in 11 per cent of patients, and include nitritoid crises, mild gastrointestinal reactions and cutaneous reactions. (3) The incidence of primary exfoliative dermatitis is 1 case in 5500 injections—about that of neoarsphenamin and less than that of other arsphenamins. (4) Three cases of jaundice have thus far been reported and no cerebral accidents. (5) Herxheimer effects are comparatively insignificant or absent. (6) The effect on the Wassermann reaction in early syphilis is excellent and lasting. (7) The proportion of all forms of relapse was 12 per cent in early syphilis as compared with from 20 to 40 per cent in a carefully studied series treated with other drugs and modern systems. (8) Intermittent is less effective than continuous treatment with the drug. Two injections a week of 0.2 gm. are preferable in early syphilis to a total of 40 to 60 treatments, usually followed by bismuth. (9) The greatest promise for bismarsen is in early syphilis. In cutaneous, mucosal and osseous gumma bismarsen is slower than other arsphenamins and is not recommended. In prenatal syphilis

the action of the drug, while not fully appraised, seems disappointing. It is not advisable in cases of interstitial keratitis because of its slowness of action. (10) Bismarsen is a safe and effective drug in the treatment of patients with the aortic types of vascular syphilis. The initial dose in such cases should not exceed 0.05 gm. (11) 50 per cent of patients with nonparetic types of neurosyphilis had blood and spinal fluid reduced to normal by mixed forms of standard treatment, preponderantly bismarsen. There was relatively little influence noted on the paretic formula in the spinal fluid. (12) Fair to good symptomatic improvement occurred in meningeal headache and lightning pains in tabes.

Erythema Infectiosum.—Lawton and Smith (*Arch. Int. Med.*, 1931, **42**, 28) report an epidemic of 97 cases of erythema infectiosum occurring in Granford, Conn. The epidemic was similar in all respects to previously reported outbreaks. Erythema infectiosum seems to be a distinct clinical entity and all evidence points to its being transmitted from person to person, although the mode of transmission and the etiology of the disease are unknown. Experimental work is cited, all of which is negative. Clinically the characteristic features are the rash, its distribution, the evanescence, the relatively long duration and the absence of symptoms. There is usually no leukocytosis but a tendency toward eosinophilia and a relative lymphocytosis.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Cancer of the Cervix.—Clinically, Deaver (*Ann. Surg.*, 1931, **94**, 381) divides cancer of the cervix into three groups: the operable, questionably operable and the inoperable. The operable group includes those where the cervix is hard and nodular, perhaps enlarged, and where the tissues are friable, but there is as yet no ulceration or evidence of metastasis. He considers these the most favorable cases for complete hysterectomy with removal of the glands with the expectation of a very low mortality. Where there is ulceration of the cervix with exuberant granulations which bleed freely to the slightest touch and there is no palpatory infiltration in the broad ligaments he uses radium and later performs complete hysterectomy. Such cases are considered questionably operable but he believes they present a fairly good temporary outlook. Sooner or later, however, most of them return with involvement of the broad ligaments and then deep Roentgen ray treatment is given but usually with little benefit. Where the entire vaginal cervix is

diseased he advises radium and deep Roentgen ray therapy and although they improve locally, eventually all die of the disease. A survey of the end results of 140 cases treated in the Lankenau Clinic shows that the expectancy of life is somewhat better after operation than after irradiation alone. The mortality of the entire group was 57.8 per cent. Eighty-three received radium only with a mortality of 70 per cent; 18 were treated by operation and radium with a mortality of 55 per cent, while the 39 treated by operation alone showed a mortality of 33.3 per cent. On the other hand, in view of the fact that many cases are hopeless when first seen, radium treatment is less distressing than operation and provides temporary improvement and he believes that radium is also of value in bringing some cases to a state of operability. Nevertheless, he is not very enthusiastic about irradiation. He has never seen an adenocarcinoma cured by this means and in the cases that have advanced to the stage of infiltration of the broad ligaments he has never seen dissipation of the infiltrate although pain has sometimes been relieved. In view of the fact that in about 40 per cent of the cases the regional glands are already cancerous when the patients come for treatment and that the radiologist cannot tell beforehand whether or not the glands are involved, he may treat cases in which radium is useless and thus deprive them of the benefits of surgery which the author believes may effect a cure in about 25 per cent of cases with glandular involvement. Therefore, he believes that the time has not yet arrived to discard surgery in the treatment of cancer of the cervix but rather give the operable cases the advantages of surgery and allow the inoperable ones the consolation of irradiation. While the opinion of such a prëeminent surgeon as Deaver is entitled to careful consideration, it should be remembered that it is at variance with the teachings of most of the larger clinics where the radical operation for cervical cancer remains only as a memory of historical interest.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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The Eye in Diabetes.—According to ASCHER (*Klin. Wchnschr.*, 1931, **10**, 1407) normally the sugar content of the aqueous is somewhat lower than that of the blood. In diabetes, the sugar content rises; but variations, either rise or fall, do not occur as rapidly as in the blood. The aqueous becomes relatively acid, loses some of its buffer substances and contains considerable acetone. These chemical changes are appar-

ently responsible for the degeneration of the posterior surface of the iris, for the variations in refraction of the lens, and for the development of diabetic cataract. Characteristic of diabetes is the edematous swelling of the pigment epithelium of the iris as a result of which pigment is set free into the aqueous in the course of intraocular operations. Rubeosis iridis, noninflammatory new vessel formation in the sphincter portion of the iris, is also characteristic of diabetes. This always leads to glaucoma. Two forms of iritis also occur, one metastatic from suppurations elsewhere in the body and another probably dependent on metabolic changes. Atropin is sometimes ineffective in the treatment of diabetic iritis, particularly during the use of insulin. Changes in pupillary reactions are very rare in diabetes; disturbances of accommodation are more frequent, due either to weakness of the ciliary muscle or to changes in the lens substance. Changes in refraction in diabetes are usually in the direction of increased myopia in the early cases and of increased hyperopia in the cases under treatment with falling blood sugar. They are due to variations in the refractive index of the lens which are most probably associated with the changing relations in concentration between the blood and the aqueous on the one hand and the lens on the other. Myopic changes in the diabetic eye may be a forerunner of cataract formation. In diabetics over 40 years the change may be a slow one, due to increasing sclerosis of the lens as in ordinary senile cataract. In younger diabetics the typical rapid cataract formation takes place as the result of increase of fluid in the cortical layers of the lens. Beginning change of this second type may remain stationary or regress under insulin therapy. They appear only in the presence of high blood sugar and acidosis. If care is taken to eliminate bacterial infection of the conjunctiva and to lower the blood sugar and rid the patient of acidosis, cataract extraction can be performed in diabetics without added risk. Intracapsular extraction is preferable. Lipemia retinalis is a rare but typical finding. The fat content of the blood varies usually between 4 per cent and 8 per cent, and acidosis is always present. It affects only the retinal, not the choroidal vessels. Retinitis is rare in diabetics under 40. It is still questionable whether vascular changes are necessary for the development of the retinitis. The central punctate retinitis of Hirschberg seems to occur at times in uncomplicated diabetes. The hemorrhagic forms are apparently always associated with high blood pressure, vessel changes and kidney damage. The basis of the retinal disease seems to be in vascular spasms which lead to disturbances of nutrition and the deposit of lipoids and fibrin. Histologically, marked changes are found in the capillaries and veins, hyalin degeneration of the walls with sclerosis and partial thromboses. In rare cases, hemorrhages take place into the vitreous with resultant retinitis proliferans. According to Onfray, about 50 per cent of patients with diabetic retinitis die within 3 years. The prognosis does not depend so much on the diabetes, however, as on the height of the blood pressure and the amount of kidney damage. In the presence of marked vessel changes insulin therapy should be used with caution. The soft eyeball which is characteristic of diabetic coma may develop before the onset of unconsciousness and may be a warning of the danger of coma. The intraocular hypotension is probably dependent on loss of fluid, especially from the vitreous rather than directly on the loss of alkali reserve from

the blood and aqueous. This view is supported by the finding of low intraocular tension in insulin hypoglycemia. Retrobulbar neuritis occurs in diabetics probably from the effect of misuse of alcohol and tobacco on an optic nerve sensitized by circulating toxic products of diabetic metabolism. It occurs more frequently in men usually over the age of 50 and is characterized by a cecocentral scotoma, especially for blue. In the treatment, withdrawal of tobacco and alcohol is necessary, as well as careful diet and insulin therapy. The disturbances of adaptation which occur frequently in diabetics may be explained on the basis of chemical changes in the pigment epithelium and in the sensory cells of the retina. Ocular muscle paralysis, affecting sometimes the third nerve but more usually the sixth, and hemianopsias are to be ascribed to accompanying high blood pressure and vascular disease rather than to the diabetes proper.

RADIOLOGY

UNDER THE CHARGE OF
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Treatment of Osteogenic Sarcoma by Means of Irradiation.—After study of 58 cases of osteogenic sarcoma treated by irradiation, and after reviewing similar work in other clinics, PFAHLER and PARRY (*Am. J. Roentgen. and Rad. Therap.*, 1931, **25**, 761) feel justified in concluding that the only two methods of treatment for this disease are irradiation or surgery or the two combined. The results from irradiation are at least equal to, and the authors believe, better than, those obtained by surgery. Preliminary irradiation of the tumor area and irradiation of the chest followed by amputation has given best results to the authors. A biopsy for diagnosis is desirable, but should be preceded by deep Roentgen therapy for a month.

Osteitis Fibrosa Cystica Generalisata With Hyperparathyroidism.—It is becoming known that hyperparathyroidism from tumor or other lesions of the parathyroids may give rise to absorption of lime salts from the bones. DRESSER and HAMPTON (*Am. J. Roentgen. and Rad. Therap.*, 1931, **25**, 739) report 2 cases and regard the condition as a form of osteitis fibrosa cystica, and consider the Roentgen picture to be characteristic. The disease affects not only the bones of the extremities but also the skull, spine, ribs and pelvis. It is seen more often in women than in men and occurs most commonly between the ages of 30 and 60 years. Pain, muscular weakness and postural abnormalities are common symptoms. Medical advice is often sought because of a spontaneous fracture. Roentgenologic changes in the affected bones are striking. In the skull, the bones of the vault present a generalized finely mottled,

granular texture, produced by closely spaced areas of diminished density which are irregular in outline and vary from a fraction of a millimeter to a centimeter or more in diameter. A similar appearance may be seen in the vertebral bodies. Often the most extensive changes are observed in the pelvis, the bones of which may show an extreme degree of decalcification with replacement of the normal bone structure by large trabeculated cystic areas. There is generalized decalcification of the ribs and occasional cystic areas associated with expansion and thinning of the cortex. The long bones present well-defined cysts which are frequently trabeculated and which may be situated anywhere in the diaphysis. In addition to the cystic areas there is generalized decalcification of the long bones with corresponding loss of density and thinning of the cortex.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Hemorrhage of the Brain.—Bowman (*Arch. Neurol. and Psychiat.*, 1931, **25**, 2) presents his investigations of hemorrhage of the brain based on cases of apoplexy in older and younger persons and on cases of gunshot wounds in which the patients lived for several hours. The major portion of his paper discusses rather well the various concepts of hemorrhage of the brain. He presents these ideas lucidly and briefly and concudes his discussion of their findings by presenting his own personal observations. In his studies he found large hemorrhages from the rupture of large vessels the rule. "There," he stated, "a disharmony existed between the blood pressure in the vessel at the moment of rupture on the one side and a weakness of the vessel wall on the other." In the cases in which weakness of the vessel wall plays the chief part, he pointed out that the ruptured vessel would generally not be the only one with a weakness of the wall, but in the adjacent area other vessels with the same alteration of the wall would be found. Normal as well as altered vessels found in the area of a hemorrhage were found ruptured. When no alteration of the vessel wall could be demonstrated, he stated that one must consider the possibility of the blood mass, which forces its way and pushes everything aside. "The blood coming from these small normal vessels and that which flows out of the degenerated vessels will greatly increase the quantity of the extravasated blood. . . . If the hemorrhage lasts longer, several factors have an influence. There may be ischemia and chemical action from the changed tissue or from the extravasated blood. Tissue reaction develops especially along the vessels; a perivasculary tissue-cell infiltration arises." In comparing other observations in several cases of apoplexy with those made in a study of gunshot wounds, the author found that

there were curious analogies between them. In a relatively short time, vessel walls with necrosis are visible in the circular space of the destruction by a gunshot wound. He found it striking that the necrobiotic process of the vessel wall was progressing from the outside to the inside—it had also begun in a tissue that according to its connective-tissue structure ought to have more resistance. Therefore, he pointed out, one must think of chemical influences of the surroundings. He found that it could be demonstrated that there was blood inside and outside the meso-ectoderm membrane, that the blood corpuscles were lying in the perivascular space of Virchow-Robin and there was transportation of blood through the glial spaces of Held. Near the gunshot wound he noticed that there was also necrosis of vessels in consequence of influences originating in the surroundings. The extravasated blood propagated through the perivascular spaces of Virchow-Robin and through the glia spaces of Held. "Thus, in both apoplexia cerebri and gunshot wounds there are mechanical and chemical influences that are of great importance." In cases of a circular hemorrhage and of poliencephalitis hemorrhagica superior there also was found a necrobiotic process of the small vessels, dependent on mechanical and chemical influences. In "red softening," tissue-cell infiltration was found, with degeneration and alteration of the vessels; this could be demonstrated in both recent and old hemorrhages. "Besides," he states, "in red softening the wall of the hemorrhage consists of three distinct layers from inside to outside: (1) brain tissue with extravasated material; (2) new-formed vessels with glia and lymphocytic elements, and (3) gliosis." He concludes his paper with the remarks, "It is not uncommon to make the clinical diagnosis of a cerebral hemorrhage and then to have the pathologist find no gross lesion at autopsy. Such cases used to be spoken of as 'hemiplegia without anatomic observations.' It is possible to explain, on a basis of transitory anemia, the various evanescent hemiplegias, monoparesis and aphasias . . .; total recovery may take place in one case, and in another that appears no worse at the beginning the neurologic signs may become permanent disabilities. In the first case there is evidently only a passing cerebral anemia, not prolonged enough to cause tissue destruction, and in the second there is actual tissue destruction of the cerebrum . . . The problem of cerebral hemorrhage is still new and challenging to investigators."

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Iodin Deficiency and Goiter.—Most American scientists accept the theory that iodin deficiency is the cause of endemic goiter. Tanabe, in Germany, claims to have produced hyperplasia of the thyroid gland

by giving white rats a diet poor in iodin. HELLIVIG (*Arch. Path.*, 1931, **11**, 709) was unable to confirm the findings of Tanabe; attempts to produce goiter in white rats by feeding a diet poor in iodin gave only negative results. His observations, on the contrary, showed that a diet poor in iodin produced atrophy of the thyroid gland. Giving a diet rich in calcium and free from iodin produced a marked epithelial hyperplasia of the thyroid gland. A diet rich in calcium and iodin produced small colloid goiters. Thus, he showed that an excess of iodin in the diet exerts an inhibitory action on hyperplasia of the thyroid gland, in spite of a high content of calcium. Thus, the author concluded that an insufficiency of iodin in the food was neither the only nor the essential cause of endemic goiter. From the positive results obtained with a diet rich in calcium, it would appear that a positive agent is responsible for the development of goiter. This positive agent may not be a single specific factor, and this or these positive agents may not alone cause hypertrophy of the thyroid gland in the presence of a high amount of iodin in the food, nor may insufficiency of iodin in itself cause endemic goiter in the absence of the other agents that cause goiter, but when both are present the conditions for the development of hyperplastic goiter would seem to be at their optimum.

The Occurrence of Intranuclear Inclusions in the Nerve Cells in Poliomyelitis.—Small intranuclear acidophilic inclusions in the nerve cells of experimental poliomyelitis, and in one human case were described by HURST (*J. Path. and Bacteriol.*, 1931, **34**, 331). Fixation of the tissues in sublimate formol or Zenker formol, with subsequent coloration by Mallory's phloxin methylene blue, was found most suitable. In poliomyelitic cords some of the anterior horn cells may be seen in a stage of degeneration characterized by a complete loss of Nissl substance, irregularity of the cell outline and often extensive vacuolation of the cytoplasm. The nucleus is enlarged and mulberry shaped, and the nucleus may appear almost or wholly devoid of any acidophilic coagulum. In such cells the author was able to find inclusion bodies most readily. In serial section the bodies were nearly always multiple; they varied in size from fine granules to rounded structures, 4 to 5 μ in diameter, appearing bright red or bluish-pink. Often a large pinkish body had small red granules adhering to its surface. The outline of the bodies was sharper than that of the nodal masses of normal acidophilic material and frequently they were separated by a clear halo from remnants of normal nuclear material. The bodies occurred in the large anterior horn cells and less often in the smaller nerve cells of the anterior and posterior horns. In addition, the nerve cells of the brain stem and the Betz cells of the motor cortex were at times affected. The bodies always occurred in damaged cells but were never seen in completely necrotic cells. The bodies were most numerous during the first three days of paralysis. The bodies were never found during the incubation period and were difficult to find late in the disease.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF
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Food Poisoning: Attempts to Immunize Human Volunteers with Staphylococcus Filtrates That Are Toxic to Man When Swallowed.—DACK, JORDAN and WOOLPERT have shown that broth filtrates prepared from certain strains of staphylococci produce symptoms of "food poisoning" (vomiting, diarrhea, weakness) when swallowed by man. Since the lower animals, including monkeys, are not visibly affected when fed with these filtrates any attempt to discover whether immunity to this toxic action can be produced is necessarily limited by the availability of human volunteers. A second attack of diarrhea can be produced in the same individual by feeding the same amount of filtrate after a week's interval. The present paper (*J. Prevent. Med.*, 1931, **5**, 151) deals with the effects observed in 5 volunteers fed with gradually increasing doses of staphylococcal filtrates of known gastrointestinal toxicity. The doses of filtrates were administered in half pints of pasteurized milk. Four human subjects fed with gradually increasing doses of staphylococcus filtrates, reaching amounts of from 25 to 32 cc., appeared to develop some tolerance to the poison of the particular strain used in the immunization treatment. Heterologous filtrates (10 cc.) taken at the conclusion of the "immunizing" treatment produced no symptoms in one subject. Two other volunteers, however, when fed respectively 2 and 10 cc. of the filtrate of a heterologous strain, developed definite symptoms, which in the person receiving the larger dose were very violent. A fifth subject was extremely sensitive to small doses of filtrate and did not develop any tolerance. Rabbits injected intravenously with gradually increasing doses of staphylococcus filtrates developed a tolerance to the staphylococcus poison, both to that of the strain used in immunization and to that of a heterologous strain. Serum from four normal persons, from a patient with active chronic osteomyelitis and from one with an old healed lesion of osteomyelitis, when injected along with staphylococcus filtrate, did not protect rabbits against the staphylococcus poison. Serum from "immunized" men and rabbits did not protect monkeys or rabbits when it was mixed with potent filtrates and injected intravenously; nor did such serum protect a human volunteer who swallowed it mixed with a potent filtrate.

An Infection of the Rocky Mountain Spotted Fever Type.—*Identification in the Eastern Part of the United States.*—BADGER, DYER and RUMREICH (*Public Health Reports*, 1931, **46**, 463) in studies on the

typhus-Rocky Mountain spotted fever group of eruptive diseases, isolated from human cases a virus very similar to that obtained from the Rocky Mountain spotted fever cases as they occur in the western states. Tests on guinea pigs, monkeys and rabbits were all successful in producing an infection of the nature mentioned. Finally cross-immunity tests were performed with a virus derived from the western Rocky Mountain spotted fever region and with the virus of typhus fever. These cross-immunity tests indicated that the new virus was not to be differentiated from the Rocky Mountain spotted fever virus and was not related to the typhus virus at least insofar as such tests may make differentiation possible.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 19, 1931

The Oxidation of Cystin by Iodin: A Consideration of Its Mechanism and of the Oxidation Reduction Potential of Thiol.—K. SHINOHARA (from the Research Institute of the Lankenau Hospital, Philadelphia). The Okuda method[1] for the determination of cystin was studied because of the ambiguous end point and the excessive consumption of iodin when the titration is conducted in low concentrations of HCl (less than 2 per cent HCl). This excessive consumption of iodin has been explained by Bierich and Kalle[2] as due to partial oxidation of cystein to cysteic acid instead of to cystin. Since bromin can effect the oxidation of disulphids to sulphonic acids, it might be expected that free iodin would do likewise. Hence the reaction between free iodin and cystin at low acidities was studied.

Investigation of the speed of the above reaction and its final equilibrium point supported the assumption that cysteic acid could be formed according to the reaction:

$$RSSR + 5I_2 + 6H_2O \rightarrow 2RSO_3 + 10HI$$

The cysteic acid was isolated and identified. A small amount of sulphuric acid was also formed.

Examination of the speed of the reaction indicated that it is probably made up of a consecutive series of bimolecular reactions. For this reason a number of hypothetical intermediate steps are proposed. Because of their instability these intermediate products have not been isolated.

The above results correspond to what would be expected from the studies of Dixon and Quastel[3] and Michaelis and Flexner[4] on the oxida-

[1] Okuda, Y. J.: Chem. Soc. Japan, 1924, **45**, 1; Chem. Abstr., 1924, **18**, 3400.
[2] Bierich, R., and Kalle, K.: Zeitschr. f. phys. Chem., 1928, **175**, 11.
[3] Dixon, M., and Quastel, J. H.: J. Chem. Soc., 1923, **123**, 2943.
[4] Michaelis, L., and Flexner, L. B.: J. Biol. Chem., 1928, **79**, 689.

tion reduction potential of the system RSSR—RSH and support the conclusion that the disulphid form is not directly in equilibrium with sulphydryl.

The Movement of Fluid Through the Human Capillary Wall in Relation to Venous Pressure and to the Colloid Osmotic Pressure of the Blood.—Eugene M. Landis (from the Robinette Foundation, University of Pennsylvania). Microinjection studies in man have shown that normal average capillary blood pressure is approximately equal to the colloid osmotic pressure of the blood. If the Starling hypothesis can be applied to fluid balance in man a relatively slight grade of venous congestion should cause the accumulation of fluid in the tissue spaces. Moreover, a rise in the colloid osmotic pressure of the blood should be accompanied by a reduction in the rate at which fluid accumulates with any given degree of venous congestion. These two points were tested by using a "pressure plethysmograph" to measure the rate at which fluid accumulated in the tissue spaces of the arm during venous congestion. Errors due to vasomotor variation were avoided, since the bloodvessels of the segment of arm within this plethysmograph were collapsed before the volume of the enclosed tissue was measured.

It was found in the normal, recumbent subject that fluid accumulated in the tissue spaces when venous pressure was greater than 15 to 20 cm. water. Above an average venous pressure of 17 cm. water the rate of filtration of fluid was directly proportional to the increase in venous pressure. A unit rise in venous pressure (1 cm. water) increased the filtration rate by 0.0023 cc. per minute per 100 cc. of arm.

The rate at which fluid was removed from the tissues of the arm depended on the size of the accumulation, being more rapid with larger collections. When the accumulated fluid amounted to less than 0.6 cc. per 100 cc. of arm the removal of fluid was retarded by elevating the venous pressure to 15 or 20 cm. water. When the accumulated fluid amounted to more than 0.6 cc. per 100 cc. of arm the fluid was removed very rapidly in spite of slight grades of venous congestion. From this it seems possible that true capillary absorption may play the dominant rôle in the removal of small accumulations of tissue fluid, while lymphatic drainage becomes more important with the larger accumulations.

When the colloid osmotic pressure of the blood was elevated by standing the rates of filtration produced by a given venous pressure were reduced below the rates observed in the same subjects when recumbent. A unit rise in colloid osmotic pressure (1 cm. water) was accompanied by a reduction in the filtration rate of from 0.0027 to 0.0045 cc. per minute per 100 cc. of arm.

Uric Acid in Frog's Glomerular Urine.—J. Bordley, 3d, and A. N. Richards (from the Physiologic Laboratory, Harvard University, School of Public Health). As a preliminary to the study of the mode of elimination of uric acid by the kidney of amphibians and reptiles, Folin's method for the quantitative estimation of this substance has been successfully adapted to such minute volumes of fluid as may be obtained by puncture of a single glomerulus of the frog's kidney. The principle of the adaptation is precisely the same as that of the original method. The reaction is conducted in a capillary tube, approximately

0.35 mm. in caliber, and the color comparison is made by the capillary tube method of Richards and Walker.

Under a low power of the microscope (15 ×), on the stage of which a micrometer scale is cemented, capillary tubes are charged with columns of fluid of measured length which are successively introduced as as follows: (*a*) Uric acid solution, 5 mm.; (*b*) cyanid urea solution, 5 mm.; (*c*) Folin's uric acid reagent, 1 mm. The tube is sealed and laid aside until the entire series, both of unknowns and standards, has been similarly prepared. When all are ready the fluids within the tubes are made to mix by whirling in a centrifuge and after an interval of 4 minutes the tubes are immersed for 1 minute in boiling water. The color comparisons are made against a brilliantly illuminated milk glass background by means of the naked eye or a reading glass.

For each series of determinations a series of 7 tubes is prepared from standard uric acid solutions as follows: 0.6, 0.8, 1.0, 1.2, 1.4, 1.6 and 2 mg. per 100 cc. If the concentration of uric acid in the unknown solution is higher than 2 mg. per 100 cc. it must be diluted appropriately to bring it into the range of the standards.

Among 39 determinations carried out in duplicate on known unknown solutions the average of the duplicates differed from the known uric acid concentration by more than 10 per cent in only 1 instance (12 per cent). The deviation from the known value was less than 5 in 74 per cent of the determinations. The average error of the 39 determinations was −1 per cent.

When 2 uric acid determinations are carried out on a single sample of glomerular urine they agree well. The technically most perfect comparisons of the uric acid content of plasma and glomerular urine collected from frogs which have been injected with uric acid indicate identity of concentration in these two fluids.

The Intermediate Hemoglobin Compound Hypothesis.—S. Goldschmidt (from the Physiologic Laboratory, Cambridge, England).

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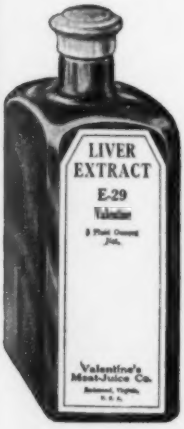

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